SPECIAL COMMUNICATION

What Makes Clinical Research Ethical?

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Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

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WHAT MAKES RESEARCH involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children,[25-29] raise questions not of informed consent, but of the ethics of subject selection, appropriate risk-benefit ratios, and the value of research to society. Since obtaining informed consent does not ensure ethical research, it is imperative to have a systematic and coherent framework for evaluating clinical studies that incorporates all relevant ethical considerations.

In this article, we delineate 7 requirements that provide such a framework by synthesizing traditional codes, declarations, and relevant literature on the ethics of research with human subjects. This framework should help guide the ethical development and evaluation of clinical studies by investigators, IRB members, funders, and others.

THE 7 ETHICAL REQUIREMENTS

The overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology[30,31]; subjects who participate are the means to securing such knowledge.[32] By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects.[33,34] Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.[30]

For the past 50 years, the main sources of guidance on the ethical conduct of clinical research have been the Nuremberg Code,[35] Declaration of Helsinki,[36] Belmont Report,[37] International Ethical Guidelines for Biomedical Research Involving Human Subjects,[38] and similar documents (TABLE 1). However, many of these documents were written in response to specific events and to avoid future scandals.[50,51] By focusing on the instigating issues, these guidelines tend to

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emphasize certain ethical requirements while eliding others. For instance, the Nuremberg Code[35] was part of the judicial decision condemning the atrocities of the Nazi physicians and so focused on the need for consent and a favorable risk-benefit ratio but makes no mention of fair subject selection or independent review. The Declaration of Helsinki[36] was developed to remedy perceived lacunae in the Nuremberg Code, especially as related to physicians conducting research with patients, and so focuses on favorable risk-benefit ratio and independent review; the Declaration of Helsinki also emphasizes a distinction between therapeutic and nontherapeutic research that is rejected or not noted by other documents.[30,52] The Belmont Report[37] was meant to provide broad principles that could be used to generate specific rules and regulations in response to US research scandals such as Tuskegee[53] and Willowbrook.[54,55] It focuses on informed consent, favorable risk-benefit ratio, and the need to ensure that vulnerable populations are not targeted for risky research. The Council for International Organizations of Medical Sciences (CIOMS) guidelines[38] were intended to apply the Declaration of Helsinki "in developing countries . . . [particularly for] large-scale trials of vaccines and drugs." The CIOMS guidelines lack a separate section devoted to risk-benefit ratios, although the council considers this issue in commentary on other guidelines. It also includes a section on compensation for research injuries not found in other documents. Because the Advisory Committee on Human Radiation Experiments was responding to covert radiation experiments, avoiding deception was among its 6 ethical standards and rules; most other major documents do not highlight this.[56] This advisory committee claims that its ethical standards are general, but acknowledges that its choices were related to the specific circumstances that occasioned the report.[56] Finally some tensions, if not outright contradictions, exist among the provisions of the various guidelines.[5,19,30,51,52,57,58] Absent a universally applicable ethical framework, investigators, IRB members, funders, and others lack coherent guidance on determining whether specific clinical research protocols are ethical.

Table 1. Selected Guidelines on the Ethics of Biomedical Research With Human Subjects*

Guideline	Source	Year and Revisions
	Fundamental	
Nuremberg Code[35]	Nuremberg Military Tribunal decision in *United States v Brandt*	1947
Declaration of Helsinki[36]	World Medical Association	1964, 1975, 1983, 1989, 1996
Belmont Report[37]	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979
International Ethical Guidelines for Biomedical Research Involving Human Subjects[38]	Council for International Organizations of Medical Sciences in collaboration with World Health Organization	Proposed in 1982; revised, 1993
	Other	
45 CFR 46, Common Rule[8]	US Department of Health and Human Services (DHHS) and other US federal agencies	DHHS guidelines in 1981; Common Rule, 1991
Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products[42]	World Health Organization	1995
Good Clinical Practice: Consolidated Guidance[44]	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	1996
Convention on Human Rights and Biomedicine[43]	Council of Europe	1997
Guidelines and Recommendations for European Ethics Committees[45]	European Forum for Good Clinical Practice	1997
Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials[46]	Medical Research Council, United Kingdom	1998
Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda[47]	Uganda National Council for Science and Technology	1998
Ethical Conduct for Research Involving Humans[48]	Tri-Council Working Group, Canada	1998
National Statement on Ethical Conduct in Research Involving Humans[49]	National Health and Medical Research Council, Australia	1999

*CFR indicates Code of Federal Regulations. More extensive lists of international guidelines on human subjects research can be found in Brody[39] and Fluss.[40] An extensive summary of US guidelines can be found in Sugarman et al.[41]

There are 7 requirements that provide a systematic and coherent framework for determining whether clinical research is ethical (TABLE 2). These requirements are listed in chronological order from the conception of the research to its formulation and implementation. They are meant to guide the ethical development, implementation, and review of individual clinical protocols. These 7 requirements are intended to elucidate the ethical standards specific for clinical research and assume general ethical obligations, such as intellectual honesty and responsibility. While none of the traditional ethical guidelines on clinical research explicitly includes all 7 requirements, these requirements systematically elucidate the fundamental protections embedded in the basic philosophy of all these documents.[30] These requirements are not limited to a specific tragedy or scandal or to the practices of researchers in 1 country; they are meant to be universal, although their application will require adaptation to particular cultures, health conditions, and economic settings. These

7 requirements can be implemented well or ineffectively. However, their systematic delineation is important and conceptually prior to the operation of an enforcement mechanism. We need to know what to enforce.

Value

To be ethical, clinical research must be valuable,[4,35] meaning that it evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being; is a preliminary etiological, pathophysiological, or epidemiological study to develop such an intervention; or tests a hypothesis that can generate important knowledge about structure or function of human biological systems, even if that knowledge does not have immediate practical ramifications.[4,30] Examples of research that would not be socially or scientifically valuable include clinical research with nongeneralizable results, a trifling hypothesis, or substantial or total overlap with proven results.[4] In addition, research with results unlikely to be disseminated or in which the intervention could never be practically implemented even if effective is not valuable.[12,13,38,59] Only if society will gain knowledge, which requires sharing results, whether positive or negative, can exposing human subjects to risk in clinical research be justified. Thus, evaluation of clinical research should ensure that the results will be disseminated, although publication in peer-reviewed journals need not be the primary or only mechanism.

There are 2 fundamental reasons why social, scientific, or clinical value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation.[4] Research resources are limited. Even if major funding agencies could fund all applications for clinical research, doing so would divert resources from other worthy social pursuits. Beyond not wasting resources, researchers should not expose human beings to potential harms without some possible social or scientific benefit.[4,30,35,38]

It is possible to compare the relative value of different clinical research studies; clinical research that is likely to generate greater improvements in health or well-being given the condition being investigated, the state of scientific understanding, and the feasibility of implementing the intervention is of higher value. Comparing relative value is integral to determinations of funding priorities when allocating limited funds among alternative research proposals.[60] Similarly, a comparative evalu-

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

ation of value may be necessary in considering studies involving finite scientific resources such as limited biological material or the small pool of long-term human immunodeficiency virus nonprogressors.

Scientific Validity

To be ethical, valuable research must be conducted in a methodologically rigorous manner.[4] Even research asking socially valuable questions can be designed or conducted poorly and produce scientifically unreliable or invalid results.[61] As the CIOMS guidelines succinctly state: "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose."[38]

For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan.[4] In addition, it must be possible to execute the proposed study. Research that uses biased samples, questions, or statistical evaluations, that is underpowered, that neglects critical end points, or that could not possibly enroll sufficient subjects cannot generate valid scientific knowledge and is thus unethical.[4,30,62] For example, research with too few subjects is not valid because it might be combined in a meaningful meta-analysis with other, as yet unplanned and unperformed clinical research; the ethics of a clinical research study cannot depend on the research that others might but have not yet done. Of course the development and approval of a valid method is of little use if the research is conducted in a sloppy or inaccurate manner; careless research that produces uninterpretable data is not just a waste of time and resources, it is unethical.

Clinical research that compares therapies must have "an honest null hypothesis" or what Freedman called clinical equipoise.[30,63] That is, there must be controversy within the scientific community about whether the new intervention is better than standard therapy, including placebo, either because most clinicians and researchers are uncertain about whether the new treatment is better, or because some believe the standard therapy is better while others believe the investigational intervention superior.[63] If there exists a consensus about what is the better treatment, there is no null hypothesis, and the research is invalid. In addition, without clinical equipoise, research that compares therapies is unlikely to be of value because the research will not contribute to increasing knowledge about the best therapy, and the risk-benefit ratio is unlikely to be favorable because some of the subjects will receive inferior treatment.

Importantly, a "good question" can be approached by good or bad research techniques; bad research methods do not render the question valueless. Thus, the significance of a hypothesis can and should be assessed prior to and independent of the specific research methods. Reviewers should not dismiss a proposal that uses inadequate methods without first considering whether adjustments could make the proposal scientifically valid.

The justification of validity as an ethical requirement relies on the same 2 principles that apply to value—limited resources and the avoidance of exploitation.[4,30] "Invalid research is unethical because it is a waste of resources as well: of the investigator, the funding agency, and anyone who attends to the research."[4] Without validity the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.[50]

Fair Subject Selection

The selection of subjects must be fair.[30,37,56] Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and the strategy adopted for recruiting subjects, such as which communities will be study sites and which potential groups will be approached. There are several facets to this requirement.

First, fair subject selection requires that the scientific goals of the study, not vulnerability, privilege, or other factors unrelated to the purposes of the research, be the primary basis for determining the groups and individuals that will be recruited and enrolled.[3,30,37] In the past, groups sometimes were enrolled, especially for research that entailed risks or offered no potential benefits, because they were "convenient" or compromised in their ability to protect themselves, even though people from less vulnerable groups could have met the scientific requirements of the study.[30,37,53,54]

Similarly, groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion.[64] It is important that the results of research be generalizable to the populations that will use the intervention. Efficiency cannot override fairness in recruiting subjects.[37] Fairness requires that women be included in the research, unless there is good reason, such as excessive risks, to exclude them.[65-69] This does not mean that every woman must be offered the opportunity to participate in research, but it does mean that women as a class cannot be peremptorily excluded.

Second, it is important to recognize that subject selection can affect the risks and benefits of the study.[70] Consistent with the scientific goals, subjects should be selected to minimize risks and enhance benefits to individual subjects and society. Subjects who are eligible based on the scientific objectives of a study, but are at substantially higher risk of being harmed or experiencing more severe harm, should be excluded from participation.[71] Selecting subjects to enhance benefits entails consideration of which subjects will maximize the benefit or value of the information obtained. If a potential drug or procedure is likely to be prescribed for women or children if proven safe and effective, then these groups should be

included in the study to learn how the drug affects them.[63,66,67] Indeed, part of the rationale for recent initiatives to include more women, minorities, and children in clinical research is to maximize the benefits and value of the study by ensuring that these groups are enrolled.[65-67,72,73] It is not necessary to include children in all phases of research. Instead, it may be appropriate to include them only after the safety of the drug has been assessed in adults.

Additionally, fair subject selection requires that, as far as possible, groups and individuals who bear the risks and burdens of research should be in a position to enjoy its benefits,[12,13,38,59,74] and those who may benefit should share some of the risks and burdens.[75] Groups recruited to participate in clinical research that involves a condition to which they are susceptible or from which they suffer are usually in a position to benefit if the research provides a positive result, such as a new treatment. For instance, selection of subjects for a study to test the efficacy of an antimalarial vaccine should consider not only who will best answer the scientific question, but also whether the selected groups will receive the benefits of the vaccine, if proven effective.[12,13,37,59,74,76] Groups of subjects who will predictably be excluded as beneficiaries of research results that are relevant to them typically should not assume the burdens so that others can benefit. However, this does not preclude the inclusion of subjects who are scientifically important for a study but for whom the potential products of the research may not be relevant, such as healthy control subjects.

Fair subject selection should be guided by the scientific aims of the research and is justified by the principles that equals should be treated similarly and that both the benefits and burdens generated by social cooperation and activities such as clinical research should be distributed fairly.[3,30,37,38,66,67] This does not mean that individual subjects and members of groups from which they are selected must directly benefit from each clinical research project c
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Clinical research involves drugs, devices, and procedures about which there is limited knowledge. As a result, research inherently entails uncertainty about the degree of risk and benefits, with earlier phase research having greater uncertainty. Clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks.[30,36,37]

Assessment of the potential risks and benefits of clinical research by researchers and review bodies typically involves multiple steps. First, risks are identified and, within the context of good clinical practice, minimized "by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes."[8]

Second, potential benefits to individual subjects from the research are delineated and enhanced. Potential benefits focus on the benefits to individual subjects, such as health improvements, because the benefits to society through the generation of knowledge are assumed if the research is deemed to be of value and valid. The specification and enhancement of potential benefits to individual subjects should consider only health-related potential benefits derived from the research.[77] Assessment of the research plan should determine if risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research. Furthermore, while participants in clinical research may receive some health services and benefits, the purpose of clinical research is not the provision of health services. Services directly related to clinical research are necessary to ensure scientific validity and to protect the well-being of the individual subjects.

In the final step, risks and potential benefits of the clinical research interventions to individual subjects are compared. In general, the more likely and/or severe the potential risks the greater in likelihood and/or magnitude the prospective benefits must be; conversely, research entailing potential risks that are less likely and/or of lower severity can have more uncertain and/or circumscribed potential benefits. If the potential benefits to subjects are proportional to the risks they face, as generally found when evaluating phase 2 and 3 research, then the additional social benefits of the research, assured by the fulfillment of the value and validity requirements, imply that the cumulative benefits of the research outweigh its risks.[30]

Obviously, the notions of "proportionality" and potential benefits "outweighing" risks are nonquantifiable.[37] However, the absence of a formula to determine when the balance of risks and potential benefits is proportionate does not connote that such judgments are inherently haphazard or subjective. Instead, assessments of risks and potential benefits to the same individuals can appeal to explicit standards, informed by existing data on the potential types

of harms and benefits, their likelihood of occurring, and their long-term consequences.[37] People routinely make discursively justifiable intrapersonal comparisons of risks and benefits for themselves and even for others, such as children, friends, and employees, without the aid of mathematical formulae.[78]

An additional evaluation is necessary for any clinical research that presents no potential benefits to individual subjects, such as phase 1 safety, pharmacokinetic, and even some epidemiology research, or when the risks outweigh the potential benefits to individual subjects.[72] This determination, which Weijer[79] calls a "risk-knowledge calculus," assesses whether the societal benefits in terms of knowledge justify the excess risks to individual subjects. Determination of when potential social benefits outweigh risks to individual subjects requires interpersonal comparisons that are conceptually and practically more difficult.[78] However, policymakers often are required to make these kind of comparisons, for example when considering whether pollution and its attendant harms to some people are worth the potential benefits of higher employment and tax revenues to others. There is no settled framework for how potential social benefits should be balanced against individual risks. Indeed, the appeal to a utilitarian approach of maximization, as in cost-benefit analysis, is quite controversial both morally and because many risks and benefits of research are not readily quantifiable on commensurable scales.[78-82] Nevertheless, these comparisons are made,[83] and regulations mandate that investigators and IRBs make them with respect to clinical research. When research risks exceed potential medical benefits to individuals and the benefit of useful knowledge to society, the clinical research is not justifiable.

The requirement for a favorable risk-benefit ratio embodies the principles of nonmaleficence and beneficence, long recognized as fundamental values of clinical research.[3,30,36,37] The principle of nonmaleficence states that one ought not to inflict harm on a person.[3] This justifies the need to reasonably reduce the risks associated with research. The principle of beneficence "refers to a moral obligation to act for the benefit of others."[3] In clinical research, this translates into the need to enhance the potential benefits of the research for both individual subjects and society.[3,30,37] Ensuring that the benefits outweigh the risks is required by the need to avoid the exploitation of subjects.[30,37]

Independent Review

Investigators inherently have multiple, legitimate interests—interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct, and analysis of research.[84-87] Wanting to complete a study quickly may lead to the use of questionable scientific methods or readily available rather than the most appropriate subjects. Independent review by individuals unaffiliated with the clinical research helps minimize the potential impact of such conflicts of interest.[86,88] For some research with few or no risks, independent review may be expedited, but for much of clinical research, review should be done by a full committee of individuals with a range of expertise who have the authority to approve, amend, or terminate a study.

Independent review of clinical research is also important for social accountability. Clinical research imposes risks on subjects for the benefit of society. Independent review of a study's compliance with ethical requirements assures members of society that people who enroll in trials will be treated ethically and that some segments of society will not benefit from the misuse of other human beings. Review also assures people that if they enroll in clinical research, the trial is ethically designed and the risk-benefit ratio is favorable.

In the United States, independent evaluation of research projects occurs through multiple groups including granting agencies, local IRBs, and data and safety monitoring boards.[89-91] In other countries, independent review of clinical research is conducted in other ways.

Informed Consent

Of all requirements, none has received as much explication as informed consent.[2-4,6,7,19,30-32,35-38] The purpose of informed consent is 2-fold: to ensure that individuals control whether or not they enroll in clinical research and participate only when the research is consistent with their values, interests, and preferences.[2,3,30-32,35,37,92-96] To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate.[97-99] Each of these elements is necessary to ensure that individuals make rational and free determinations of whether the research trial is consonant with their interests.

Informed consent embodies the need to respect persons and their autonomous decisions.[2,3,97,98] To enroll individuals in clinical research without their authorization is to treat them merely as a means to purposes and ends they may not endorse and deny them the opportunity to choose what projects they will pursue.

Children and adults with diminished mental capacity who are unable to make their own decisions about participating in research nonetheless have interests and values.[2,3] For instance, individuals rendered unconscious due to head trauma or a stroke typically retain the interests and values they had just before the accident. Even individuals with severe Alzheimer disease retain some interests, if only those related to personal dignity and physical comfort. Showing respect for these nonautonomous persons means ensuring that research participation is consistent with their interests and values; this

usually entails empowering a proxy decision maker to determine whether to enroll the person in clinical research. In making this decision, the proxy uses the substituted judgment standard: what research decision would the subject make if he or she could.[2,3,100]

However, an individual's preferences and values related to clinical research may be unknown or unknowable, or, in the case of children, the individual may not have developed mature preferences related to research. In such cases, research proxies should choose the option that is in the individual's best medical interests. There is controversy about how much discretion proxies should have in such circumstances, especially given the inherent uncertainty of the risks and potential benefits of research participation.[101-105] The National Bioethics Advisory Commission has urged that proxies should exercise "great caution" in making judgments about a subject's best interest regarding research.[103] Other groups believe that proxies should have more discretion.

In emergency settings that preclude time for identifying and eliciting the consent of a proxy decision maker, research can proceed without either informed consent or permission of proxy decision makers when conducted under strict guidelines.[6] Most importantly, there should be clinical equipoise—the absence of a consensus regarding the comparative merits of the interventions to be tested.[63] In such a case, the subject is not worse off by enrolling.

Respect for Potential and Enrolled Subjects

Ethical requirements for clinical research do not end when individuals either sign the consent form and are enrolled or refuse enrollment.[106] Individuals must continue to be treated with respect from the time they are approached—even if they refuse enrollment—throughout their participation and even after their participation ends. Respecting potential and enrolled subjects entails at least 5 different activities. First, since substantial information will be collected about potential as well as enrolled subjects, their privacy must be respected by managing the information in accordance with confidentiality rules. Second, respect includes permitting subjects to change their mind, to decide that the research does not match their interests, and to withdraw without penalty. Third, in the course of clinical research new information about the effect of the intervention or the subject's clinical condition may be gained. Respect requires that enrolled subjects be provided with this new information. For instance, when informed consent documents are modified to include additional risks or benefits discovered in the course of research, subjects already enrolled should be informed. Fourth, the welfare of subjects should be carefully monitored throughout their research participation. If subjects experience adverse reactions, untoward events, or changes in clinical status, they should be provided with appropriate treatment and, when necessary, removed from the study. Finally, to recognize subjects' contribution to clinical research, there should be some mechanism to inform them of what was learned from the research.

For commentators used to thinking about respect in terms of privacy and confidentiality alone, these different activities may seem a haphazard agglomeration of informed consent, confidentiality, and other protections. In fact, this requirement integrates into a coherent framework actions the commonality of which often goes unrecognized. As such, it reminds investigators, subjects, IRB members, and others that respect for subjects requires the respectful treatment of individuals who choose not to enroll and the careful ongoing monitoring of those who do, in addition to ensuring the privacy and confidentiality of enrolled subjects. This requirement emphasizes that the ethics of clinical research do not end with the signing of a consent document but encompass the actual implementation, analysis, and dissemination of research. Indeed, it suggests that although "human subjects" is the prevailing designation, the term *subject* may not fully reflect appropriate respect: human research participant or partner may be more appropriate terminology.

Respect for potential and enrolled subjects is justified by multiple principles including beneficence, nonmaleficence, and respect for persons.[3] Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy.[3,37] Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and nonmaleficence.[3]

ARE THESE ETHICAL REQUIREMENTS NECESSARY AND SUFFICIENT?

Value, validity, fair subject selection, favorable risk-benefit ratio, and respect for subjects embody substantive ethical values. As such, they are all necessary: clinical research that neglected or violated any of these requirements would be unethical. Conversely, independent review and informed consent are procedural requirements intended to minimize the possibility of conflict of interest, maximize the coincidence of the research with subjects' interests, and respect their autonomy.[30] However, other procedures may also achieve these results. For instance, evidence of an individual's preferences regarding research may be obtained from a research advance directive rather than the individual's concurrent informed consent.[103] Given the existence of alternative procedures, informed consent requirements can be minimized, and, in some circumstances, consent can even be waived.[7,101,103] Research on emergency life-saving interventions for subjects who are unconscious or otherwise not mentally capable of consent and for whom family or proxy consent is not immediately available may be conducted without informed consent.[6,107-109] Thus, all requirements need to be satisfied, but they may have to be adjusted and balanced given the circumstances of different types of research.

As interpreted and elaborated for specific research protocols, the fulfillment of each of these 7 requirements ensures that research is socially valuable and subjects are not exploited, that subjects are treated fairly and with respect, and that their interests are protected. As a result, these requirements should be sufficient to ensure that the vast majority of clinical research is ethical.[30] While it may be impossible to exclude the possibility that additional requirements are needed in rare cases, these 7 requirements are the essential ones.

UNIVERSALITY OF THE REQUIREMENTS

These 7 requirements for ethical clinical research are also universal.[35-49,110] They are justified by ethical values that are widely recognized and accepted and in accordance with how reasonable people would want to be treated.[110-112] Indeed, these requirements are precisely the types of considerations that would be invoked to justify clinical research if it were challenged.

Like constitutional provisions and amendments, these ethical requirements are general statements of value that must be elaborated by traditions of interpretation and that require practical interpretation and specification that will inherently be context and culture dependent.[110-113] For instance, while informed consent is meant to ensure that research subjects are treated with respect, what constitutes respect varies from culture to culture.[110,114] In some places, it will be necessary to elicit the consent of elders before individual subjects can be approached for informed consent.[115] Similarly, who is considered vulnerable for the purposes of fair subject selection criteria will vary by locale. While in the United States special efforts are necessary to ensure that racial minorities are not just targeted for research with high potential for risks,[53,73] in other places fair subject selection may require special focus on religious groups. Similarly, local traditions and economic conditions will influence when financial payments may constitute undue inducements. Also, whether research has a favorable risk-benefit ratio will depend on the underlying health risks in a society. Research that is unacceptable in one society because its risks outweigh the risks posed by the disease may have a favorable risk-benefit ratio in another society where the risks posed by the disease are significantly greater. Adapting these requirements to the identities, attachments, and cultural traditions embedded in distinct circumstances neither constitutes moral relativism nor undermines their universality[110-112]; doing so recognizes that while ethical requirements embody universal values, the manner of specifying these values inherently depends on the particular context.[110-112]

NECESSARY EXPERTISE

These ethical requirements emphasize the type of training and skills necessary for clinical investigators and those conducting independent review (Table 2). Not only must clinical investigators be skilled in the appropriate methods, statistical tests, outcome measures, and other scientific aspects of clinical trials, they must have the training to appreciate, affirm, and implement these ethical requirements, such as the capacity and sensitivity to determine appropriate subject selection criteria, evaluate risk-benefit ratios, provide information in an appropriate manner, and implement confidentiality procedures. Similarly, because independent review of clinical research must assess its value, validity, selection criteria, risk-benefit ratios, informed consent process, and procedures for monitoring enrolled subjects, the necessary skills must range from scientific to ethical to lay knowledge. Consequently, the independent ethical review of research trials should involve individuals with training in science, statistics, ethics, and law, as well as reflective citizens who understand social values, priorities, and the vulnerability and concerns of potential subjects (Table 2).

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cal evaluation of clinical research. One persistently controversial issue is the use of placebo controls.[14-16] A new class of antiemetics, serotonin antagonists, such as ondansetron hydrochloride and granistron hydrochloride, were developed about 10 years ago. To evaluate these drugs, investigators conducted placebo-controlled trials randomizing cancer patients receiving emetogenic chemotherapy to either placebo or the serotonin antagonists.[116-118]

In evaluating the ethics of this clinical research, all requirements need to be fulfilled, but 3 requirements seem particularly relevant: value, scientific validity, and risk-benefit ratio. There is no doubt that the dominant antiemetic therapies of the time, such as prochlorperazine, metoclopramide hydrochloride, and high-dose corticosteroids are effective. However, they are not completely effective, especially for strongly emetogenic chemotherapy such as platinum, and they have significant adverse effects, especially dystonic reactions. Alternative antiemetic therapies that would be more effective and have fewer adverse effects were viewed as desirable and of value. However, there was no value in knowing whether the serotonin antagonists were better than placebo in controlling emesis, since placebo was not the standard of care at the time of the research.[14,63] Even if the serotonin antagonists were shown to be more effective than placebo, it would be a further issue to evaluate their effectiveness and adverse-event profile compared with the extant interventions. Thus, a placebo-controlled trial of the serotonin antagonists for chemotherapy-induced emesis does not fulfill the value requirement.

Comparative studies evaluating the difference between 2 active treatments are common in cancer therapy and valid as a study design.[14-16] Some argue that active-controlled studies are scientifically more difficult to conduct than placebo-controlled trials.[119] However, any ethically and scientifi-

placebo was not reasonable at the time of the clinical research.[14,63] Indeed, coeval with the placebo-controlled studies were randomized controlled trials with serotonin antagonists vs active antiemetic therapy.[120,121] Thus, a placebo-controlled trial was not the only scientifically valid method.

Those who supported the notion of a randomized, placebo-controlled trial of serotonin antagonists argued that there was no serious risk from using a placebo because emesis is a transitory discomfort that results in no permanent disability.[119,122] However, emesis is not pleasant. Indeed, the entire rationale for developing serotonin antagonists is that chemotherapy-induced emesis is a sufficiently serious health problem that development and use of effective interventions in clinical practice are justifiable and desirable.[123] As one published report of a randomized placebo-controlled trial of ondansetron stated to justify the research: "Uncontrolled nausea and vomiting [from chemotherapy] frequently results in poor nutritional intake, metabolic derangements, deterioration of physical and mental condition, as well as the possible rejection of potentially beneficial treatment. Many patients are more afraid of uncontrolled nausea and vomiting than of alopecia."[118]

Furthermore, the placebo-controlled trials for antiemetics included "'rescue' medication if patients had persistent nausea or vomiting."[118] This indicates both that there was an alternative standard treatment for chemotherapy-induced emesis and that emesis was sufficiently harmful to require intervention.[14,15,123,124] Permitting patients to vomit while being administered placebo causes them unnecessary harm.[14,123,124] Thus, a placebo-controlled trial of antiemetics for chemotherapy-induced emesis does not minimize harm in the context of good clinical practices and so fails the favorable risk-benefit ratio when an available clinical intervention can partially ameliorate some of the harm.[123]

Importantly, the evaluation of these placebo-controlled trials of antiemetics did not need to address informed consent to determine whether they were ethical.[122] Indeed, even if patients had signed an informed consent document that indicated they could be randomized to placebo and that there were alternative effective treatments, the placebo-controlled research on serotonin antagonists would still be unethical.

Another controversial issue involves research in developing countries.[9-13,57,59] Recently, a rhesus rotavirus tetravalent (RRV-TV) vaccine was licensed in the United States after randomized trials in developed countries demonstrated a 49% to 68% efficacy in preventing diarrhea and up to 90% efficacy in preventing severe cases of diarrhea.[125-127] However, shortly after approval, the vaccine was withdrawn from the US market because of a cluster of cases of intussusception, representing an approximately 1 in 10 000 added risk of this complication.[128] Should randomized controlled trials of RRV-TV vaccine proceed as planned in developing countries or wait for a new vaccine candidate to be developed? (C. Weijer, MD, PhD, written communication, March 24, 2000) In evaluating the ethics of these proposed trials, the requirements of value, scientific validity, fair subject selection, and risk-benefit ratio are particularly relevant.

Despite oral rehydration therapy, more than 600 000 children in developing countries die annually from rotavirus diarrhea.[129] In some countries, the death rate from rotavirus is nearly 1 in 200. Clearly, a rotavirus vaccine with even 80% efficacy that prevented more than half a million deaths would be of great value. But is research using the RRV-TV vaccine ethical when the risk of intussusception stopped its use in the United States? The RRV-TV vaccine was the first and only licensed rotavirus vaccine and has already been administered to nearly 1 million children; potential alternative rotavirus vaccines are still years away from phase 3 research. Thus, given the potential benefit of preventing deaths from rotavirus in developing countries, a trial of RRV-TV vaccine now—even if a better vaccine becomes evaluable in a few years—is worthwhile. There is value to the research on the vaccine for developing countries only if there is reasonable assurance children in the country would be able to obtain it if it proved effective.[12,13,59]

Vaccines effective in developed countries may or may not be as effective or safe in developing countries. Host, viral, and environmental factors and seasonality of the disease can alter the efficacy and safety profiles of a vaccine.[130] Thus, there is good scientific rationale for determining whether the RRV-TV vaccine can achieve sufficient levels of protection against diarrhea with an acceptably low incidence of complications in children in developing countries. In this case, given the lack of an established method of preventing rotavirus infections in these countries, a placebo-controlled trial would be valid.

Two factors suggest that, in the RRV-TV vaccine study, subjects in developing countries are being selected for reasons of science and not being exploited. First, the most appropriate subjects for a rotavirus vaccine trial are infants and children who have a high incidence of rotavirus infection and who experience significant morbidity and mortality from the infection. In such a population the efficacy of the vaccine would be most apparent. Second, since the RRV-TV vaccine has been withdrawn from the US market, children in developing countries are not being selected to assume risks to evaluate a vaccine that will ultimately benefit children in developed countries (Weijer, written communication). As long as the RRV-TV vaccine would be made available to the population recruited for the study if proven safe and effective, children in the developing countries are being selected appropriately.[12,13,59]

The final element is evaluation of the risk-benefit ratio. In the United States, the RRV-TV vaccine posed a risk of intussusception of about 1 in 10 000, while rotavirus causes about 20 deaths annually or in fewer than 5 in 1 million children. Thus, in developed countries the risk-benefit ratio is not favorable—1 death from rotavirus diarrhea pre-

vented at the risk of 20 to 40 cases of intussusception. Because of underlying disease burden, the risk-benefit ratio in developing countries is much different. If rotavirus causes the death of 1 in 200 children while the RRV-TV vaccine causes intussusception in 1 in 10000 children, about 50 deaths from rotavirus diarrhea are prevented for each case of intussusception. Consequently, the risk-benefit ratio of the RRV-TV vaccine is favorable for individual subjects in developing countries while it is unfavorable for subjects in developed countries. This difference in risk-benefit ratios is a fundamental part of the justification for conducting the research on an RRV-TV vaccine in a developing country when it could not be ethically conducted in a developed country (Weijer, written communication). Obviously, to be ethical, randomized controlled trials of an RRV-TV vaccine would also have to adhere to the other requirements—independent review, informed consent, and respect for enrolled subjects.

CONCLUSION

These 7 requirements for considering the ethics of clinical research provide a systematic framework to guide researchers and IRBs in their assessments of individual clinical research protocols. Just as constitutional rulings are rarely unanimous, this framework will not necessarily engender unanimous agreement on the ethics of every clinical research study. Reasonable disagreement results from 3 sources: differences of interpretations of the requirements, of views about the need for additional requirements, and of application to specific studies. Nevertheless, this framework does provide the necessary context for review bodies to generate traditions of interpretation, understand disagreements, and highlight the kinds of considerations that must be invoked to resolve them. Like a constitution, these requirements can be reinterpreted, refined, and revised with changes in science and experience. Yet these requirements must all be considered and met to ensure that clinical research—wherever it is practiced—is ethical.

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REFERENCES

1. Childress J. The place of autonomy in bioethics. *Hastings Cent Rep*. 1984;14:12-16.
2. Dworkin G. *The Theory and Practice of Autonomy*. New York, NY: Cambridge University Press; 1988.
3. Beauchamp TL, Childress J. *The Principles of Biomedical Ethics*. New York, NY: Oxford University Press; 1996:chap 3.
4. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:45-58.
5. Freedman B. Scientific value and validity as ethical requirements for research. *IRB*. 1987;9:7-10.
6. Office of the Secretary. Protection of human subjects: informed consent and waiver of informed consent requirements in certain emergency research; final rules. 61 *Federal Register* 51498-51533 (1996).
7. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med*. 1999;340:804-807.
8. US Department of Health and Human Services. Protections of human subjects. 45 CFR §46 (1991).
9. Angell M. The ethics of clinical research in the third world. *N Engl J Med*. 1997;337:847-849.
10. Lurie P, Wolfe S. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med*. 1997;337:853-856.
11. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med*. 1997;337:1003-1005.
12. Grady C. Science in the service of healing. *Hastings Cent Rep*. 1998;28:34-38.
13. Crouch R, Arras J. AZT trials and tribulations. *Hastings Cent Rep*. 1998;28:26-34.
14. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med*. 1994;331:394-398.
15. Freedman B. Placebo-controlled trials and the logic of clinical purpose. *IRB*. 1990;12:1-6.
16. Weijer C. Placebo-controlled trials in schizophrenia. *Schizophr Res*. 1999;35:211-218.
17. Lipsett M. On the nature and ethics of phase I clinical trials of cancer chemotherapies. *JAMA*. 1982;248:941-942.
18. Freedman B. Cohort-specific consent. *IRB*. 1990;12:5-7.
19. Annas GJ. The changing landscape of human experimentation. *Health Matrix*. 1992;2:119-140.
20. Lehrman S. Jewish leaders seek guidelines. *Nature*. 1997;389:322.
21. Levine C, Dubler NN, Levine RJ. Building a new consensus. *IRB*. 1991;13:1-17.
22. Weijer C, Goldsand G, Emanuel EJ. Protecting communities in research. *Nat Genet*. 1999;23:275-280.
23. Juengst ET. Groups as gatekeepers to genomic research. *Kennedy Institute J Ethics*. 1998;8:183-200.
24. Weijer C. Protecting communities in research. *Camb Q Healthc Ethics*. 1999;8:501-513.
25. Kopelman LM, Moskop JC, eds. *Children and Health Care*. Dordrecht, the Netherlands: Klumer; 1989:73-87.
26. Freedman B, Fuks A, Weijer C. In loco parentis. *IRB*. 1993;15:13-19.
27. Leikin S. Minors' assent, consent, or dissent to medical research. *IRB*. 1993;15:1-7.
28. Grodin MA, Glantz LH, eds. *Children as Research Subjects*. New York, NY: Oxford University Press; 1994:81-101.
29. Committee on Drugs, American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics*. 1995;95:286-294.
30. Levine RJ. *Ethics and Regulation of Clinical Research*. 2nd ed. New Haven, Conn: Yale University Press; 1988.
31. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Summing Up*. Washington, DC: US Government Printing Office; 1983.
32. Katz J. *Experimentation With Human Beings*. New York, NY: Russell Sage Foundation; 1972.
33. Wertheimer A. *Exploitation*. Princeton, NJ: Princeton University Press; 1996: chap 1.
34. DeCastro LD. Exploitation in the use of human subjects for medical experimentation. *Bioethics*. 1995;9:259-268.
35. The Nuremberg Code. *JAMA*. 1996;276:1691.
36. World Medical Association. Declaration of Helsinki. *JAMA*. 1997;277:925-926.
37. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. Washington, DC: US Government Printing Office; 1979.
38. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: CIOMS; 1993.
39. Brody BS. *The Ethics of Biomedical Research*. New York, NY: Oxford University Press; 1998:chap 9.
40. Fluss S. *International Guidelines on Bioethics*. Geneva, Switzerland: European Forum on Good Clinical Practice/CIOMS; 1998.
41. Sugarman J, Mastroianni A, Kahn JP. *Research With Human Subjects*. Frederick, Md: University Publishing Group; 1998.
42. World Health Organization. Guidelines for good clinical practice for trials on pharmaceutical products. In: *The Use of Essential Drugs*. Appendix 3. Geneva, Switzerland: WHO; 1995.
43. Council of Europe (Direcorate of Legal Affairs). *Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine*. Strasbourg, France: Council of Europe; 1996.
44. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Good clinical practice: consolidated guidance, 62 *Federal Register* 25692 (1997).
45. European Forum for Good Clinical Practice. *Guidelines and Recommendations for European Ethics Committees*. Leuven, Belgium: EFGCP; 1997.
46. Medical Research Council (UK). *Guidelines for Good Clinical Practice in Clinical Trials*. London, England: MRC; 1998.
47. Uganda National Council of Science and Technology (UNCST). *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda*. Kampala, Uganda: UNCST; 1998.
48. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement*. Ottawa, Ontario: Public Works and Government; 1998.
49. National Health and Medical Research Council. *National Statement on Ethical Conduct in Research Involving Humans*. Canberra, Australia: NHMRC; 1999.
50. Levine RJ. The impact of HIV infection on society's perception of clinical trials. *Kennedy Institute J Ethics*. 1994;4:93-98.

51. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:235-260.
52. Levine RJ. The need to revise the Declaration of Helsinki. *N Engl J Med*. 1999;341:531-534.
53. Jones J. *Bad Blood*. New York, NY: Free Press; 1992.
54. Rothman D, Rothman S. *The Willowbrook Wars*. New York, NY: Harper & Row; 1984.
55. Krugman S. The Willowbrook hepatitis studies revisited. *Rev Infect Dis*. 1986;8:157-162.
56. Advisory Committee on Human Radiation Experiments. *The Human Radiation Experiments*. New York, NY: Oxford University Press; 1996.
57. Christakis N, Panner M. Existing international ethical guidelines for human subjects. *Law Med Health Care*. 1991;19:214-220.
58. Lasagna L. The Helsinki declaration. *J Clin Psychopharmacol*. 1995;15:96-98.
59. Glantz LH, Annas GJ, Grodin MA, et al. Research in developing countries. *Hastings Cent Rep*. 1998;28:38-42.
60. Committee on the NIH Research Priority-Setting Process. *Scientific Opportunities and Public Needs*. Washington, DC: National Academy Press; 1998.
61. Rutstein DD. The ethical design of human experiments. In: Fruend PA, ed. *Experimentation With Human Subjects*. New York, NY: Braziller Library; 1970: 383-402.
62. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Appendix*. Vol 1. Washington, DC: US Government Printing Office; 1978:chap 9.
63. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317:141-145.
64. National Institutes of Health. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Available at: http://grants.nih.gov/grants/guide/notice-files/not98-024.html. Accessed April 28, 2000.
65. Dresser R. Wanted: single, white male for medical research. *Hastings Cent Rep*. 1992;22:21-29.
66. Merton V. The exclusion of pregnant, pregnable, and once pregnable (a.k.a. women) from biomedical research. *Am J Law Med*. 1993;19:369-451.
67. DeBruin D. Justice and the inclusion of women in clinical studies. *Kennedy Institute J Ethics*. 1994;4: 117-146.
68. Mastriani AC, Faden RR, Federman DD. *Women and Health Research*. Washington, DC: National Academy Press; 1994.
69. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:105-126.
70. Weijer C. Evolving issues in the selection of subjects for clinical research. *Camb Q Healthc Ethics*. 1996; 5:334-345.
71. Weijer C, Fuks A. The duty to exclude. *Clin Invest Med*. 1994;17:115-122.
72. Merkatz RB, Temple R, Sobel S, et al. Women in clinical trials of new drugs. *N Engl J Med*. 1993;329: 292-296.
73. National Institutes of Health. NIH Guidelines for the inclusion of women and ethnic minorities in research, 59 *Federal Register* 14508-14513 (1994).
74. Barry M, Molyneux M. Ethical dilemmas in malaria drug and vaccine trials. *J Med Ethics*. 1992;18: 189-192.
75. Kahn J, Mastroianni A, Sugarman J. *Beyond Consent*. New York, NY: Oxford University Press; 1998.
76. Annas G, Grodin M. Human rights and maternal-fetal HIV transmission prevention trials in Africa. *Am J Public Health*. 1998;88:560-563.
77. Freedman B, Fuks A, Weijer C. Demarcating research and treatment. *Clin Res*. 1992;40:653-660.
78. Anderson E. *Value in Ethics and Economics*. Cambridge, Mass: Harvard University Press; 1993:chap 9.
79. Weijer C. Thinking clearly about research risks. *IRB*. 1999;21:1-5.
80. Sen A, Williams B, eds. *Utilitarianism and Beyond*. Cambridge, England: Cambridge University Press; 1982.
81. MacLean D, ed. *Values at Risk*. Totowa, NJ: Rowman & Allanheld; 1985:31-48.
82. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
83. Sen A. *Choice, Welfare, and Measurement*. Cambridge, Mass: Harvard University Press; 1982:264-284.
84. Relman AS. Economic incentives in clinical investigations. *N Engl J Med*. 1989;320:933-934.
85. Porter RJ, Malone TE. *Biomedical Research*. Baltimore, Md: Johns Hopkins University Press; 1992.
86. Thompson D. Understanding financial conflicts of interest. *N Engl J Med*. 1993;329:573-576.
87. Spece RG, Shimm DS, Buchanan AE. *Conflicts of Interest in Clinical Practice and Research*. New York, NY: Oxford University Press; 1996.
88. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Institutional Review Boards*. Washington, DC: US Government Printing Office; 1978.
89. Curran WJ. Government regulation of the use of human subjects in medical research. In: Freund PA, ed. *Experimentation With Human Subjects*. New York, NY: George Braziller; 1970:402-455.
90. Edgar H, Rothman D. The institutional review board and beyond. *Milbank Q*. 1995;73:489-506.
91. Moreno J, Caplan AL, Wolpe PR, et al. Updating protections for human subjects involved in research. *JAMA*. 1998;280:1951-1958.
92. Fried C. *Medical Experimentation*. New York, NY: American Elsevier Co; 1974.
93. Freedman B. A moral theory of informed consent. *Hastings Cent Rep*. 1975;5:32-39.
94. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research. *Making Health Care Decisions*. Washington, DC: US Government Printing Office; 1982.
95. Katz J. Human experimentation and human rights. *St Louis University Law J*. 1993;38:1-54.
96. Donagan A. Informed consent in therapy and experimentation. *J Med Philos*. 1977;2:318-329.
97. Faden RR, Beauchamp TL. *A History and Theory of Informed Consent*. New York, NY: Oxford University Press; 1986:chap 5-9.
98. Applebaum PA, Lidz CW, Meisel A. *Informed Consent*. New York, NY: Oxford University Press; 1987.
99. Grisso R, Applebaum PS. *Assessing Competence to Consent to Treatment*. New York, NY: Oxford University Press; 1998.
100. Buchanan AE, Brock DW. *Deciding for Others*. New York, NY: Cambridge University Press; 1990: chap 2.
101. American College of Physicians. Cognitively impaired subjects. *Ann Intern Med*. 1989;111:843-848.
102. Dresser R. Mentally disabled research subjects. *JAMA*. 1996;276:67-72.
103. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity*. Washington, DC: US Government Printing Office; 1998.
104. Michels R. Are research ethics bad for our mental health? *N Engl J Med*. 1999;340:1427-1430.
105. Capron AM. Ethical and human rights issues in research on mental disorders that may affect decision-making capacity. *N Engl J Med*. 1999;340:1430-1434.
106. Weijer C, Shapiro S, Fuks A, Glass KC, Skrutkowska M. Monitoring clinical research. *CMAJ*. 1995; 152:1973-1980.
107. Biros MH, Lewis R, Olson C, et al. Informed consent in emergency research. *JAMA*. 1995;273:1283-1287.
108. Levine RJ. Research in emergency situations. *JAMA*. 1995;273:1300-1302.
109. Council on Ethical and Judicial Affairs, American Medical Association. *Waiver of Informed Consent for Emergency Research*. CEJA Report 1-A-7, June 1997.
110. Macklin R. *Against Relativism*. New York, NY: Oxford University Press; 1999.
111. Scanlon TM. *What We Owe to Each Other*. Cambridge, Mass: Harvard University Press; 1999: chap 1, 8.
112. Kymlicka W. *Liberalism, Community and Culture*. New York, NY: Oxford University Press; 1989.
113. Angell M. Ethical imperialism? *N Engl J Med*. 1988;319:1081-1083.
114. Levine RJ. Informed consent. *Law Med Health Care*. 1991;19:207-213.
115. Ijsselmuiden CB, Faden RR. Research and informed consent in Africa. *N Engl J Med*. 1992;326: 830-833.
116. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;322:810-816.
117. Gandara DR, Harvey WH, Monaghan GG, et al. The delayed-emesis syndrome from cisplatin. *Semin Oncol*. 1992;19:67-71.
118. Beck TM, Ciociola AA, Jones SE, et al. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med*. 1993;118:407-413.
119. Temple R. Government viewpoint of clinical trials. *Drug Inform J*. 1982:1610-1617.
120. Marty M, Pouillart P, Scholl S, et al. Comparison of 5-hydroxytryptamine3 (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med*. 1990;322:816-821.
121. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol*. 1991;9:721-728.
122. Ondansetron and cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;323:1486.
123. Hait WN. Ondansetron and cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;323:1485-1486.
124. Citron ML. Placebos and principles. *Ann Intern Med*. 1993;118:470-471.
125. Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high dose rhesus-human reassortant rotavirus vaccines. *Pediatrics*. 1996;97:7-13.
126. Bernstein DK, Glass RI, Rodgers G, et al. Evaluation of rhesus rotavirus monovalent and tetravalent reassortment vaccines in US children. *JAMA*. 1995; 273:1191-1196.
127. Joensuu J, Koskenniemi E, Pang XL, Vesikari T. Randomized placebo-controlled trial of rhesus-human reassortment rotavirus vaccine for prevention of severe rotavirus gastroenteritis. *Lancet*. 1997; 350:1205-1209.
128. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48:577-581.
129. Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrheal disease. *Bull World Health Organ*. 1992;70:705-714.
130. Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine*. 1999;17:2207-2222.

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Treatment of Central Precocious Puberty

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Long-acting analogs of GnRH (GnRHas) have been the gold-standard treatment of central precocious puberty (CPP) worldwide and have an enviable track record of safety and efficacy. Recent years have witnessed much growth in the availability of longer-acting and sustained-release forms of GnRHas. Although all available agents appear promising, limited long-term follow-up and/or comparative data are available. In this review, important issues pertaining to the treatment of children with CPP are discussed. In addition to an assessment of the newer extended-release GnRHa formulations, a delineation of factors essential in determining which children should be treated is offered. Outstanding uncertainties in clinical management are highlighted and areas in need of future research identified. Literature searches for this review were performed in PubMed and OVID, with a focus on English-language publications using the terms "central precocious puberty" and "treatment."

Freeform/Key Words: precocious puberty, treatment, GnRH analogs

Central precocious puberty (CPP) refers to early activation of the hypothalamic-pituitary-gonadal (HPG) axis and occurs in 1 in 5000 to 10,000 children [1]. CPP is far more common in girls, in whom it is usually idiopathic. Safe and effective treatment of CPP in the form of long-acting GnRH analogs (GnRHas) has been available for many years [2].

The development of GnRHas was based on the recognition that sustained high concentrations of GnRH resulted in a paradoxical downregulation and subsequent suppression of the HPG axis [3]. In the early 1980s, several different formulations of GnRHas were developed with different durations of action and routes of administration. Historically, the most commonly used preparation in the United States for the treatment of CPP was monthly IM depot leuprolide [4]. However, during the past decade or so, there has been a substantial increase in the number of extended-release formulations of GnRHas, resulting in a broad array of therapeutic options for patients and providers. These include 3-monthly (*i.e.*, once every 3 months) depot IM preparations, 6-monthly (*i.e.*, once every 6 months) depot IM preparations, and a subcutaneous implant that is marketed for annual use [5].

Although these longer-acting formulations are expected to improve compliance, the cost of GnRHas developed for use in children has remained extremely high. While minimal comparative information about the extended-release options is available in the short term, how they will stack up in contrast to monthly depot leuprolide regarding long-term safety and efficacy. Despite the excellent track record achieved in the arena of pharmacologic treatment of CPP, several notable queries remain about clinical management of affected children. These include criteria for treatment, the role of psychological considerations, whether brain MRI scanning should be mandatory, how therapy should be monitored, and when it should be discontinued. This review discusses each of the extended-release GnRHa formulations

Abbreviations: CNS, central nervous system; CPP, central precocious puberty; GnRHa, GnRH analog; HPG, hypothalamic-pituitary-gonadal.

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currently in the therapeutic armamentarium, describes areas of uncertainly in clinical management, and highlights unanswered questions and future directions.

1. Extended-Release GnRHa Preparations

A. Three-Monthly Depot GnRHas

Although 3-monthly depot GnRHas have been used in Europe for the treatment of CPP for many years [6], the first US Food and Drug Administration approval of a 3-monthly form of depot leuprolide for pediatric use occurred in 2011. While clinical indices of pubertal suppression have been reassuring, the 11.25-mg 3-monthly dose resulted in <100% HPG-axis suppression in several studies. These have included trials investigating 1- vs 3-monthly depot leuprolide [7, 8], a 3-year study of two different doses of depot leuprolide [9], and a meta-analysis of 3-monthly triptorelin for 1 year [10]. In contrast, one small retrospective study found no differences in adult height between girls treated with monthly vs 3-monthly triptorelin at the 11.25-mg dose [11]. Longer and larger-scale follow-up studies are needed to determine if there are meaningful discrepancies in clinical outcomes resulting from different doses of 3-monthly GnRHas as compared with monthly treatment.

B. Six-Monthly Depot GnRHas

A 6-monthly form of depot triptorelin was approved in 2017 by the US Food and Drug Administration for use in CPP. This approval was based on findings from an international, multicenter study conducted in 44 patients [12]. Appropriate HPG-axis suppression was noted in 93% of the subjects at 6 months and in 97.7% at 12 months. As with 3-monthly preparations, parameters indicating efficacy in terms of pubertal progression were favorable. However, given the limited amount of information available, no firm conclusions can be made yet about 6-monthly depot GnRHas. Trials investigating additional 6-monthly preparations besides triptorelin are underway.

C. Subcutaneous Histrelin Implant

A subcutaneous implant containing 50 mg of the potent GnRHa histrelin has been available for the treatment of CPP since 2007. Constructed of a soft hydrogel, the device releases histrelin at a rate of ~65 μg/d and results in profound HPG-axis suppression within 1 month [13]. The implant is typically inserted in the upper inner arm using local anesthesia in most cases [14]. After 5 years of treatment, predicted adult heights in children naïve to treatment increased by 9 to 10 cm [15]. Although marketed for annual use, the recognition that a single implant lasts at least 2 years has the potential to decrease costs and numbers of surgical procedures in children treated with this modality [16]. Routes of administration, available doses, and duration of action of each of the extended-release GnRHa preparations available for use in the United States are summarized in Table 1.

Table 1. Extended-Release Preparations of GnRH Analogs Available in the United States

Generic Name	Brand Name (Manufacturer)	Route of Administration	Available Doses (mg)	Duration of Action
3-Monthly leuprolide	Lupron Depot-PED 3 mo (AbbVie, Chicago, IL)	IM	11.25, 30	3 mo
6-Monthly triptorelin	Triptodur (Arbor Pharmaceuticals, Atlanta, GA)	IM	22.5	6 mo
Histrelin implant	Supprelin LA (Endo Pharmaceuticals, Malvern, PA)	Subcutaneous implant	50	≥2 y

doi: 10.1210/js.2019-00036 | Journal of the Endocrine Society | 967

2. Safety of GnRHas

GnRHas have an admirable safety profile. The most commonly reported adverse events are injection-site reactions which are typically mild and self-limited. However, sterile abscess formation has been reported in the setting of IM injections [17] and the histrelin implant [18]. The most problematic issue encountered with the histrelin implant is a propensity for the device to fracture during explanation, which in rare cases has necessitated ultrasound guidance to remove remaining fragments [19]. During treatment, growth velocity can significantly decline, particularly in patients with a markedly advanced bone age. This may necessitate addition of adjunctive treatment in the form of GH or oxandrolone [20]. Although some children may experience weight gain while on therapy, the preponderance of evidence suggests that GnRHas do not have a negative effect on body mass index in patients being treated for CPP [21, 22]. Bone mineral density is typically increased for age at diagnosis and progressively decreases during GnRHa treatment. However, follow-up of patients several years after cessation of therapy reveals bone mineral accrual to be within the normal range compared with population norms [23].

3. Criteria for Treatment

The main goal of treatment in children with CPP is the preservation of height potential. Although this sounds straightforward, any consideration of height outcomes must acknowledge several limitations. One is that no randomized controlled studies examining the effect of treatment vs no treatment on height in CPP have ever been conducted, to this author's knowledge. Another is that outcome in terms of height is generally based on the difference between predicted adult height at diagnosis and ultimate adult height at the end of treatment [24–28]. By definition, height predictions are based on bone-age radiographs, which are highly imprecise and subject to substantial variability in interpretation. In addition, bone ages typically over-predict height in CPP [29]. Thus, it is very difficult to accurately predict height outcome for any individual child. In addition to the caveats already mentioned, the degree of height gained also depends on multiple factors, including chronological age, pubertal stage, skeletal maturation, and tempo of pubertal development. It has long been recognized that a subset of children with CPP have a slowly progressive form of early puberty that does not benefit from intervention in terms of adult height [30]. The challenge lies in identifying which patients will ultimately belong in this category as compared with those who will lose a substantial degree of height potential without treatment. Therefore, a period of observation of ~6 months has been recommended unless puberty is quite advanced (Tanner stage ≥3 breast development in girls) at initial presentation [31]. Paradoxically, the suggestion to wait for some time before initiating therapy is in direct contradiction to the observation that the benefit gained in terms of height is inversely proportional to the age at which treatment is started. Girls in whom GnRHa therapy is initiated at age ≤6 years derive the greatest benefit from intervention, whereas those who are treated at between 6 and 8 years have a variable outcome [32, 33]. In contrast, no increase in adult height is seen in girls who are treated after age 8 years [34, 35]. Despite broad acknowledgment of a lack of increase in adult stature in girls treated when they are older than 8 years, GnRHa treatment continues to be initiated in many children who are well above this age threshold [36]. This likely reflects parental anxiety regarding impending menses as well as effective marketing by the producers of GnRHas. Insufficient data regarding boys with CPP have hampered the establishment of analogous age cutoffs for treatment efficacy in boys. The other concern often used as a rationale for treatment is negative psychosocial consequences of precocious puberty, particularly in girls. Because of conflicting conclusions in the medical literature in this area, no clear consensus regarding the risk of psychopathology in children with CPP exists [37]. Although some studies have indicated increased stress and anxiety in girls with CPP [38, 39], others have found no differences in psychological functioning as compared with control subjects [40, 41]. This is an area in which more research is

968 | Journal of the Endocrine Society | doi: 10.1210/js.2019-00036

definitely needed. Table 2 summarizes the results of several studies reporting adult height outcomes in girls treated for CPP.

4. Controversies in Management of CPP

A. Need for Brain MRI

Once a diagnosis of CPP has been made, clinicians are faced with the decision of whether to order a brain MRI. This decision only pertains to girls, because the much higher rate of intracranial pathology mandates central nervous system (CNS) imaging in all boys with CPP. It has been suggested that brain MRI scanning may not be necessary in girls older than age 6 years who have no neurologic symptoms [42]. However, others have advocated for routine brain MRIs regardless of age, because of the finding of CNS abnormalities in girls with CPP who are older than age 6 years [43]. Potential consequences of unnecessary MRIs include cost, parental anxiety, and need for repeated imaging when incidental findings are uncovered. A meta-analysis of MRI findings in children with CPP revealed a total prevalence of CNS lesions of 9%, which decreased to 7% when only those possibility related to early puberty were included [44]. Notably, however, only 1.6% of these required intervention, because the vast majority were hypothalamic hamartomas which respond to medical therapy. Given that a small risk of important CNS abnormalities does exist, it is unlikely that the controversy surrounding this aspect of management will be resolved any time soon. For now, the recommendation is to discuss the pros and cons of MRI scanning with parents and allow them to participate in the decision of whether or not to pursue this test [45].

In children with a family history of CPP, genetic testing for an *MKRN3* mutation, the most common monogenetic cause of precocious puberty, will likely supersede CNS imaging, rendering this issue moot in many cases [46]. A second genetic etiology underlying familial CPP is deletions in *DLK1*, which encodes for Delta-Like 1 Homolog [47]. Both *MKRN3* and *DLK1* are maternally imprinted genes that are expressed only from the paternal allele. Thus, a family history of CPP on the father's side should increase the index of suspicion for a

Table 2. Examples of Studies Reporting Adult Height in Girls Treated With a GnRHa for CPP

First Author	Year of Publication	No. of Girls Participating	Modality Used and Duration of GnRH Treatment[a]	Adult Height Achieved, Mean ± SD (cm)	Height Increase Above Predicted at Baseline (cm)
Heger [24]	1999	50	Depot triptorelin 4.4 ± 2.1 y	160.6 ± 8.0	5.7
Antoniazzi [25]	2000	71	Depot triptorelin, buserelin nasal spray 16–56 mo	154.4 ± 5.6	2-7
Lazar [32]	2007	115	Depot decapeptyl 2.8–4.8 y	160.35 ± 5.05	5
Pasquino [26]	2008	87	Depot triptorelin 4.2 ± 1.6 y	159.8 ± 5.3	5.1
Nabhan [27]	2009	26	Depot leuprolide 3.6 ± 2.1 y	163 ± 7.6	4.5
Magiakou [22]	2010	33	Depot triptorelin 2.75 y	158.5	6.95
Poomthavorn [21]	2011	47	Depot leuprolide or triptorelin 3.4 ± 1.5 y	158.6 ± 5.2	4.7
Bertelloni [11]	2015	25	Depot triptorelin, 3.05 ± 0.9 y	158.25 ± 5.8	3
Lee [28]	2018	84	Depot leuprolide 2.98 ± 0.73 y	160.1 ± 5	4

[a]Duration data reported as mean ± SD or as a range.

doi: 10.1210/js.2019-00036 | Journal of the Endocrine Society | 969

mutation in one of these genes. Other genetic causes of CPP include activating mutations in kisspeptin and its receptor, *KISS1R* [48, 49]. However, each of these has been described as causing CPP in only a single patient thus far [50].

B. Monitoring of Treatment

There is no systematic strategy for monitoring whether adequate suppression of the HPG axis has been achieved in children being treated for CPP [51]. Although there is unanimity regarding the value of auxologic indices such as growth velocity, Tanner staging, and skeletal maturation, no agreement exists on the need for biochemical measures of treatment efficacy [52]. In fact, unexpected pitfalls are sometimes encountered when assumptions are made about hormonal studies in CPP. A case in point is the use of random ultrasensitive LH concentrations, which are helpful in the diagnosis of CPP and were postulated to adequately reflect HPG-axis suppression during treatment. Unexpectedly, random ultrasensitive LH values frequently remain in the pubertal range in children receiving GnRHa therapy that otherwise provides adequate HPG-axis suppression, and therefore these values can be misleading [53, 54]. Given the lack of evidence for any association between biochemical monitoring and adult height, it is reasonable to forgo any routine blood testing in children being treated for CPP. If treatment failure is suspected on clinical grounds, a GnRHa stimulation test is recommended.

C. Discontinuation of Therapy

A final area of uncertainty in the management of CPP relates to the optimal age of discontinuation of treatment. There are essentially no studies in which age at treatment cessation has been standardized. However, cumulative evidence suggests that optimal height gains are realized when treatment is stopped at a bone age of ~12 years in girls and ~13 years in boys [37, 55, 56]. Regardless, the decision of when to halt therapy is individualized and incorporates numerous patient-specific characteristics including absolute and predicted height, chronological age, psychosocial factors, pubertal stage, and family preferences.

D. Gonadal Function After GnRHa Therapy

Information regarding long-term outcomes of patients treated with GnRHas with respect to gonadal function are reassuring. Unsurprisingly, the vast majority of existing data pertain only to women. Menstrual cycles are reported to be normal with respect to duration and timing, and mean ovarian volumes similar to those in the general population. There have been no perceived health consequences to offspring of mothers who were treated with GnRHas and no increased need for assisted reproductive technology [57, 58]. Limited follow-up in adolescent boys previously treated with a GnRHa for CPP reveals similarly normal testicular function and sperm counts within the normal range [59], although more data in men are needed.

5. Conclusion

The therapeutic armamentarium for the treatment of children with CPP has rapidly expanded, resulting in the availability of several newer extended-release GnRHa formulations. Although the efficacy and safety of these longer-acting agents are not expected to diverge from historically used preparations, only a modicum of information regarding some of them is available. Likewise, a lack of head-to-head comparison data renders it impossible to determine whether any relative superiority among these different treatment options exists. Despite the highly favorable treatment profile of CPP in general, there are several unresolved questions pertaining to clinical management of affected children. Areas particularly in need of additional research include psychological sequelae of CPP and height outcomes in boys.

Efforts aimed at determining the optimal strategy for monitoring treatment and time for discontinuation of GnRHa therapy are also needed.

Acknowledgments

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References and Notes

1. Sultan C, Gaspari L, Maimoun L, Kalfa N, Paris F. Disorders of puberty. *Best Pract Res Clin Obstet Gynaecol*. 2018;**48**:62–89.
2. Comite F, Cutler GB, Jr, Rivier J, Vale WW, Loriaux DL, Crowley WF, Jr. Short-term treatment of idiopathic precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. A preliminary report. *N Engl J Med*. 1981;**305**(26):1546–1550.
3. Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. *Science*. 1978;**202**(4368): 631–633.
4. Swerdloff RS, Heber D. Superactive gonadotropin-releasing hormone agonists. *Annu Rev Med*. 1983; **34**:491–500.
5. Aguirre RS, Eugster EA. Central precocious puberty: From genetics to treatment. *Best Pract Res Clin Endocrinol Metab*. 2018;**32**(4):343–354.
6. Carel JC, Blumberg J, Seymour C, Adamsbaum C, Lahlou N; Triptorelin 3- month CPP Study Group. Three-month sustained release triptorelin (11.25 mg) in the treatment of central precocious puberty. *Eur J Endocrinol*. 2006;**154**(1):119–124.
7. Fuld K, Chi C, Neely EK. A randomized trial of 1- and 3-month depot leuprolide doses in the treatment of central precocious puberty. *J Pediatr*. 2011;**159**(6):982–7.e1.
8. Mericq V, Lammoglia JJ, Unanue N, Villaroel C, Hernández MI, Avila A, Iñiguez G, Klein KO. Comparison of three doses of leuprolide acetate in the treatment of central precocious puberty: preliminary results. *Clin Endocrinol (Oxf)*. 2009;**71**(5):686–690.
9. Lee PA, Klein K, Mauras N, Lev-Vaisler T, Bacher P. 36-Month treatment experience of two doses of leuprolide acetate 3-month depot for children with central precocious puberty. *J Clin Endocrinol Metab*. 2014;**99**(9):3153–3159.
10. Durand A, Tauber M, Patel B, Dutailly P. Meta-analysis of paediatric patients with central precocious puberty treated with intramuscular triptorelin 11.25 mg 3-month prolonged-release formulation. *Horm Res Paediatr*. 2017;**87**(4):224–232.
11. Bertelloni S, Massart F, Einaudi S, Wasniewska M, Miccoli M, Baroncelli GI. Central precocious puberty: adult height in girls treated with quarterly or monthly gonadotropin-releasing hormone analog triptorelin. *Horm Res Paediatr*. 2015;**84**(6):396–400.
12. Klein K, Yang J, Aisenberg J, Wright N, Kaplowitz P, Lahlou N, Linares J, Lundström E, Purcea D, Cassorla F. Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty. *J Pediatr Endocrinol Metab*. 2016;**29**(11):1241–1248.
13. Eugster EA, Clarke W, Kletter GB, Lee PA, Neely EK, Reiter EO, Saenger P, Shulman D, Silverman L, Flood L, Gray W, Tierney D. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab*. 2007;**92**(5):1697–1704.
14. Davis JS, Alkhoury F, Burnweit C. Surgical and anesthetic considerations in histrelin capsule implantation for the treatment of precocious puberty. *J Pediatr Surg*. 2014;**49**(5):807–810.
15. Silverman LA, Neely EK, Kletter GB, Lewis K, Chitra S, Terleckyj O, Eugster EA. Long-term continuous suppression with once-yearly histrelin subcutaneous implants for the treatment of central precocious puberty: a final report of a phase 3 multicenter trial. *J Clin Endocrinol Metab*. 2015;**100**(6): 2354–2363.
16. Lewis KA, Goldyn AK, West KW, Eugster EA. A single histrelin implant is effective for 2 years for treatment of central precocious puberty. *J Pediatr*. 2013;**163**(4):1214–1216.
17. Johnson SR, Nolan RC, Grant MT, Price GJ, Siafarikas A, Bint L, Choong CS. Sterile abscess formation associated with depot leuprorelin acetate therapy for central precocious puberty. *J Paediatr Child Health*. 2012;**48**(3):E136–E139.

18. Miller BS, Shukla AR. Sterile abscess formation in response to two separate branded long-acting gonadotropin-releasing hormone agonists. *Clin Ther*. 2010;**32**(10):1749–1751.
19. Rosati S, Maarouf R, Brown K, Poppe M, Parrish D, Haynes J, Lanning D. Histrelin for central precocious puberty-a single surgeon experience. *J Surg Res*. 2015;**198**(2):355–359.
20. Vottero A, Pedori S, Verna M, Pagano B, Cappa M, Loche S, Bernasconi S, Ghizzoni L. Final height in girls with central idiopathic precocious puberty treated with gonadotropin-releasing hormone analog and oxandrolone. *J Clin Endocrinol Metab*. 2006;**91**(4):1284–1287.
21. Poomthavorn P, Suphasit R, Mahachoklertwattana P. Adult height, body mass index and time of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing hormone analogue treatment. *Gynecol Endocrinol*. 2011;**27**(8):524–528.
22. Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanaka-Gantenbein C, Piaditis G, Chrousos GP, Dacou-Voutetakis C. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab*. 2010;**95**(1):109–117.
23. Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term outcomes of the treatment of central precocious puberty. *Eur J Endocrinol*. 2016;**174**(3):R79–R87.
24. Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab*. 1999;**84**(12):4583–4590.
25. Antoniazzi F, Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Borrelli P, Osio D, Mengarda F, De Luca F, Tatò L. End results in central precocious puberty with GnRH analog treatment: the data of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab*. 2000;**13**(Suppl 1):773–780.
26. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab*. 2008;**93**(1):190–195.
27. Nabhan ZM, Feezle LK, Kunselman AR, Johnson NB, Lee PA. Normal adult height among girls treated for central precocious puberty with gonadotropin-releasing hormone analog therapy. *J Pediatr Endocrinol Metab*. 2009;**22**(4):309–316.
28. Lee HS, Yoon JS, Park KJ, Hwang JS. Increased final adult height by gonadotropin-releasing hormone agonist in girls with idiopathic central precocious puberty. *PLoS One*. 2018;**13**(8):e0201906.
29. Lopes MC, Ramos CO, Latronico AC, Mendonça BB, Brito VN. Applicability of a novel mathematical model for the prediction of adult height and age at menarche in girls with idiopathic central precocious puberty. *Clinics (São Paulo)*. 2018;**73**:e480.
30. Palmert MR, Malin HV, Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. *J Clin Endocrinol Metab*. 1999;**84**(2):415–423.
31. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnukainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M, Wit JM; ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;**123**(4):e752–e762.
32. Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *J Clin Endocrinol Metab*. 2007;**92**(9):3483–3489.
33. Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. *Hum Reprod Update*. 2004;**10**(2):135–147.
34. Bertelloni S, Massart F, Miccoli M, Baroncelli GI. Adult height after spontaneous pubertal growth or GnRH analog treatment in girls with early puberty: a meta-analysis. *Eur J Pediatr*. 2017;**176**(6):697–704.
35. Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-effective gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. *Horm Res Paediatr*. 2018;**90**(1):1–7.
36. Watson SE, Greene A, Lewis K, Eugster EA. Bird's-eye view of GnRH analog use in a pediatric endocrinology referral center. *Endocr Pract*. 2015;**21**(6):586–589.
37. Ehrhardt AA, Meyer-Bahlburg HF. Psychosocial aspects of precocious puberty. *Horm Res*. 1994;**41**(Suppl 2):30–35.
38. Mercader-Yus E, Neipp-López MC, Gómez-Méndez P, Vargas-Torcal F, Gelves-Ospina M, Puerta-Morales L, León-Jacobus A, Cantillo-Pacheco K, Mancera-Sarmiento M. Anxiety, self-esteem and body image in girls with precocious puberty [in Spanish]. *Rev Colomb Psiquiatr*. 2018;**47**(4):229–236.

39. Menk TAS, Inácio M, Macedo DB, Bessa DS, Latronico AC, Mendonca BB, Brito VN. Assessment of stress levels in girls with central precocious puberty before and during long-acting gonadotropin-releasing hormone agonist treatment: a pilot study. *J Pediatr Endocrinol Metab*. 2017;**30**(6):657–662.
40. Schoelwer MJ, Donahue KL, Didrick P, Eugster EA. One-year follow-up of girls with precocious puberty and their mothers: do psychological assessments change over time or with treatment? *Horm Res Paediatr*. 2017;**88**(5):347–353.
41. Schoelwer MJ, Donahue KL, Bryk K, Didrick P, Berenbaum SA, Eugster EA. Psychological assessment of mothers and their daughters at the time of diagnosis of precocious puberty. *Int J Pediatr Endocrinol*. 2015;**2015**(1):5.
42. Pedicelli S, Alessio P, Scirè G, Cappa M, Cianfarani S. Routine screening by brain magnetic resonance imaging is not indicated in every girl with onset of puberty between the ages of 6 and 8 years. *J Clin Endocrinol Metab*. 2014;**99**(12):4455–4461.
43. Mogensen SS, Aksglaede L, Mouritsen A, Sørensen K, Main KM, Gideon P, Juul A. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. *PLoS One*. 2012;**7**(1):e29829.
44. Cantas-Orsdemir S, Garb JL, Allen HF. Prevalence of cranial MRI findings in girls with central precocious puberty: a systematic review and meta-analysis. *J Pediatr Endocrinol Metab*. 2018;**31**(7):701–710.
45. Kaplowitz PB. Do 6-8 year old girls with central precocious puberty need routine brain imaging? *Int J Pediatr Endocrinol*. 2016;**2016**(1):9.
46. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol*. 2016;**4**(3):265–274.
47. Dauber A, Cunha-Silva M, Macedo DB, Brito VN, Abreu AP, Roberts SA, Montenegro LR, Andrew M, Kirby A, Weirauch MT, Labilloy G, Bessa DS, Carroll RS, Jacobs DC, Chappell PE, Mendonca BB, Haig D, Kaiser UB, Latronico AC. Paternally inherited DLK1 deletion associated with familial central precocious puberty. *J Clin Endocrinol Metab*. 2017;**102**(5):1557–1567.
48. Silveira LG, Noel SD, Silveira-Neto AP, Abreu AP, Brito VN, Santos MG, Bianco SD, Kuohung W, Xu S, Gryngarten M, Escobar ME, Arnhold IJ, Mendonca BB, Kaiser UB, Latronico AC. Mutations of the KISS1 gene in disorders of puberty. *J Clin Endocrinol Metab*. 2010;**95**(5):2276–2280.
49. Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S, Seminara SB, Mendonca BB, Kaiser UB, Latronico AC. A GPR54-activating mutation in a patient with central precocious puberty. *N Engl J Med*. 2008;**358**(7):709–715.
50. Cantas-Orsdemir S, Eugster EA. Update on central precocious puberty; From etiologies to outcomes. *Expert Rev Endocrinol Metab*. 2019;**14**(2):123–130.
51. Chen M, Eugster EA. Central precocious puberty: update on diagnosis and treatment. *Paediatr Drugs*. 2015;**17**(4):273–281.
52. Zung A, Burundukov E, Ulman M, Glaser T, Zadik Z. Monitoring gonadotropin-releasing hormone analogue (GnRHa) treatment in girls with central precocious puberty: a comparison of four methods. *J Pediatr Endocrinol Metab*. 2015;**28**(7-8):885–893.
53. Lewis KA, Eugster EA. Random luteinizing hormone often remains pubertal in children treated with the histrelin implant for central precocious puberty. *J Pediatr*. 2013;**162**(3):562–565.
54. Neely EK, Silverman LA, Geffner ME, Danoff TM, Gould E, Thornton PS. Random unstimulated pediatric luteinizing hormone levels are not reliable in the assessment of pubertal suppression during histrelin implant therapy. *Int J Pediatr Endocrinol*. 2013;**2013**(1):20.
55. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, Chaussain JL. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. *J Clin Endocrinol Metab*. 1999;**84**(6):1973–1978.
56. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol*. 2016;**4**(3):265–274.
57. Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y. Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades. *Clin Endocrinol (Oxf)*. 2014;**80**(4):570–576.
58. Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev*. 2014;**11**(3):306–317.
59. Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr*. 2000;**159**(5):369–374.

ORIGINAL ARTICLE

Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data

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Context: To date, there are few studies investigating the impact of body changes induced by cross-sex hormonal treatment (CHT) on psychobiological well-being in gender-dysphoric persons (GDs).

Objective: The objective of the study was to assess whether CHT-related body changes affect psychobiological well-being in GDs.

Methods: A consecutive series of 359 GDs was considered for a cross-sectional section of the study. In addition, 54 GDs were studied in a 2-year follow-up. A physical examination was performed, including body mass index, waist circumference, and hair distribution. We also evaluated breast development and testis volume in male to female subjects and clitoris length in female to male. Subjects were asked to complete several psychometric measures for the assessment of body uneasiness, GD, and psychopathology levels. The evaluation was repeated 2 years prospectively.

Results: The following results were found: 1) GDs undergoing CHT reported significantly lower subjective levels of GD, body uneasiness, and depressive symptoms as compared with those without; 2) CHT-induced body modifications were significantly associated with a better psychological adjustment; 3) during CHT, GDs reported a significant reduction of general psychopathology, depressive symptoms, and subjective GD, whereas social and legal indicators of GD showed a significant increase across time; and 4) among body changes induced by CHT, only breast development and increased body mass index had a significant impact on psychopathology reduction across time in male to female subjects and female to male subjects, respectively.

Conclusions: The aforementioned results support the efficacy of CHT intervention in improving subjective perception of one's own body, which was partially associated with objective changes. (*J Clin Endocrinol Metab* 101: 4260–4269, 2016)

Gender dysphoria (GD) is characterized by a marked incongruence between one's experienced/expressed gender and the assigned one, associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning (1). Because GD can occur with different levels of intensity, a flexible approach in treatment should be offered (2–5).

Regarding interventions aimed at reducing the discrepancy between body and gender identity, a medical approach should include cross-sex hormonal treatment

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Abbreviations: ANCOVA, analysis of covariance; BDI, Beck Depression Inventory; BMI, body mas index; BUT, Body Uneasiness Test; CHT, cross-sex hormonal treatment; FG, Ferriman and Gallwey; GIDYQ-AA, Gender Identity/Gender Dysphoria questionnaire; FtM, female to male; GD, gender dysphoria; GRS, genital reassignment surgery; GSI, global severity index; MtF, male to female; SCL-90-R, Symptom Checklist 9

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(CHT) alone or together with genital reassignment surgery (GRS) (2).

To date, most studies have focused on the positive effects of GRS on mental and sexual health and satisfaction (6–13). Only recently have studies evaluated the potential benefits derived from CHT alone on psychological well-being (4, 14–17). A meta-analysis on sex reassignment shows that CHT alone reduces GD and improves quality of life and psychological and psychosocial well-being (18). More recently, other studies have shown similar results, reporting that CHT is associated with a better quality of life (19, 20), reduction of psychiatric comorbidity (15, 21), lower social distress (21), less body dissatisfaction (4), and an improved sex life (14).

However, among the aforementioned studies, only one (15) has prospectively analyzed psychiatric comorbidity in those with GD as a function of CHT, with a 12-month follow-up, with all the others being derived from cross-sectional evaluation. Furthermore, to date, there are no longitudinal studies that highlight a direct connection of CHT with body dissatisfaction and GD levels.

Considering that, for ethical issues, it is not possible to perform a randomized, placebo-controlled study (with a no-CHT control group), we performed a double-design study with a cross-sectional comparison between GD persons (GDs) vs no CHT at baseline and a prospective intervention study on the effect of CHT across time.

Materials and Methods

Aims

According to the aforementioned design, the main aims of the present study were to evaluate the following: 1) the differences in terms of psychological well-being between persons with vs no CHT (cross-sectional study); 2) whether gender-related body features may correlate with psychopathology (cross-sectional study); 3) the psychobiological effect of CHT over time (prospective study); and 4) the impact of different body changes in psychopathology modification over time (prospective study).

Design of the study

All subjects included were diagnosed with GD according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (1), as specified below. Two different studies were performed based on the reported previous CHT.

Cross-sectional study

Participants

Subjects referring for the first time to the center for GD assistance at the University of Florence were enrolled in the cross-sectional study, provided they met the following inclusion criteria: age older than 18 years and diagnosis of GD based on formal psychiatric classification criteria and performed through several sessions with two different mental health professionals specialized in GD.

The exclusion criteria were as follows: GRS performed; illiteracy; mental retardation; and disorder of sexual development

A total of 178 subjects were excluded from the initial sample because of the following reasons: changes in CHT prior to the study (n = 53), mental retardation (n = 1), dropout during assessment (n = 23), completed GRS (n = 78), disorder of sexual development (n = 3), or absence of GD diagnosis (three had internalized homophobia, seven transvestite fetishism, three personality disorder, and seven had gender nonconformity diagnosis). The selected sample included 359 participants, of which 140 (39.0%) were female to male (FtM) and 219 (61.0%) male to female (MtF). Supplemental Figure 1 reports the details of the participants in a flow chart.

Prospective study

Participants

A subsample of patients enrolled in the cross-sectional study, referring to the center for GD assistance at the University of Florence from September 2012 to August 2015, were enrolled in the prospective study (Supplemental Figure 1), provided they met the following inclusion criteria: a request for GRS at the time of inclusion and a request to start CHT.

The use at any point in life of CHT and augmentation mammoplasty were considered the exclusion criteria for the prospective analysis.

A total of 54 participants were included before CHT start and evaluated at 3 (T1), 6 (T2), 12 (T3), and 24 months (T4) after CHT prescription. Of the included sample, 28 (51.9%) were MtFs and 26 (48.1%) FtMs. All MtFs received oral cyproterone acetate (50 mg) combined with oral estradiol valerate (66.7%) or transdermal estradiol (33.3%). All FtMs received testosterone undecanoate 1000 mg im, with the first injection repeated after 6 weeks, and then after 12 weeks. The injection interval was adjusted (normally between 10–14 wk) based on serum T levels with the aim of obtaining hormone levels in the normal reference range for males. All patients received standardized professional mental health support every 3 months.

Measures

Sociodemographic data

Subjects reported their sociodemographic information and previous cosmetic surgery interventions. Information was also collected regarding estrogen and/or antiandrogen treatment and patients' gender role.

Anthropometric measures

Anthropometric measurements were made by expert endocrinologists using standard calibrated instruments. In particular, patients underwent a complete physical examination, with measurement of height, weight, waist, and body mass index (BMI). Testis volume in MtFs was evaluated using a Prader orchidometer (22). Breast development during the CHT in MtFs was assessed according to Tanner staging (5). The degree of hair growth was assessed by the same endocrinologist (A.D.F.) according to the modified Ferriman and Gallwey (FG) scoring system (23). The score was then adjusted in MtFs by asking the patient to describe medium hair density during the last 2 weeks before

depilation or waxing. Total stretched clitoral length was measured as the distance from the tip of the glans to the point at the symphysis pubis at which the crura are thought to insert, thus including the clitoral body and glans (24).

Blood samples were drawn in the morning for the determination of glutamic-oxaloacetic transaminase and glutamic-pyruvate transaminase and were measured in a subsample of patients included in the cross-sectional study using routine clinical chemistry methods.

Psychometric evaluations

In addition, patients were asked to complete several psychometric tests, such as the Body Uneasiness Test (BUT) (25), the Symptom Checklist 90 revised (SCL-90-R) (26), the Gender Identity/Gender Dysphoria questionnaire (GIDYQ-AA) (27), and the Beck Depression Inventory (BDI) II (28).

A description of the aforementioned questionnaires has been reported in Supplemental Table 2.

Finally, physical (breast development, BMI, FG score, testis volume) and psychological (BUT-global severity index [GSI]) change ratios were calculated dividing the difference of score at T4 and T0 by the score at T0.

The study protocol was approved by the institution's ethics committee. All the patients have provided their written informed consent to participate to the study

Statistical analyses

Continuous variables were reported as mean ± SD, whereas categorical variables were reported as a percentage. For the assessment of between-group differences (CHT vs no-CHT groups), a χ^2 and an independent measures *t* test were applied for categorical and continuous variables, respectively. Differences between groups were evaluated in a multivariate model (adjusting for relevant clinical confounders) by means of an analysis of covariance (ANCOVA). Linear regression analyses were performed to assess the associations of continuous clinical variables. Linear mixed models (ANOVA mixed model with random intercept) were adopted for longitudinal data. In particular, these models were used to study the variation (time effect) of clinical variables within different time points. Paired-sample *t* tests were adopted to evaluate differences from one time point to another.

Results

Cross-sectional study

Sociodemographic and clinical characteristics of the cross-sectional sample according to CHT

Individuals from the CHT group (n = 167) were significantly older than in the no-CHT (n = 192; age ±SD 33.90 ± 9.19 and 29.11 ± 9.28 y, respectively; t = −4.76, $P \leq .0001$).

On average, MtFs (n = 125) and FtMs (n = 42) reported 1331 (31; 13 445) and 323 (33; 1095) days of hormone therapy, respectively.

Regarding the type of CHT, in the FtM group, 76.2% (n = 32) were using parenteral testosterone enanthate, 33.3% (n = 14) parenteral testosterone undecanoate, and 33.3% (n = 14) transdermal testosterone. For the MtF group, 44.0% (n = 55) was using oral estradiol valerate, 26.4% (n = 33) oral ethinyl estradiol, 28% (n = 35) transdermal estradiol hemihydrate, 19.2% (n = 24) estradiol gel, 3.2% (n = 4) oral finasteride, 4.0% (n = 5) oral dutasteride, 78.4% (n = 98) oral cyproterone acetate, and 1.6% (n = 2) oral spironolactone.

For eight MtFs and three FtMs in the CHT group, we did not have information on the type of treatment.

It should be noted that self-medication was often the reason for the mixed CHT profile of some subjects (eg, more than one type of estrogen formulation at the same time), as previously reported (4).

BMI was 23 ± 4.02 and 24.4 ± 3.61 kg/m^2, respectively, for MtFs and FtMs. Moreover, 54.8% of MtFs and 12.8% of FtMs reported any kind of cosmetic surgery.

For those patients with available information on liver function (n = 103), no significant differences were found in transaminase levels between CHT and no-CHT persons, in both MtFs and FtMs (see Supplemental Table 3).

Differences in terms of psychological well-being between persons with vs without CHT

Table 1 reports psychological characteristics of both groups and their differences in an age-, gender role-, and cosmetic surgery-adjusted ANCOVA models.

Considering depressive symptoms in FtMs, BDI-II levels were significantly lower in the CHT vs no-CHT group. For MtFs, this figure does not reach statistical difference (9.41 ± 7.91 and 7.31 ± 8.55 in no-CHT and CHT FtMs, respectively; $P = .027$). In addition, significantly lower levels of body uneasiness were observed in the CHT group in both genders, as compared with no-CHT. Regarding the GIDYQ-AA total score, CHT individuals showed significantly higher levels of global GD. However, when GIDYQ-AA subscales were considered in MtFs, the subjective GD was significantly higher in the CHT sample vs no-CHT. An opposite figure was found in the CHT group vs no-CHT for legal and social GDs, which were significantly lower, respectively, in FtMs and MtFs.

Psychopathological correlates of gender-related body features

Considering MtFs, after adjustment for the aforementioned confounders (age, cosmetic surgery, and gender role) and for BMI, the FG score was significantly associated with higher levels of subjective GD (GIDYQ-AA, $\beta = -0.334$, $P = .049$, Figure 1A), body uneasiness (BUT-GSI, $\beta = .445$, $P = .002$, Figure 1B), and with a tendency of increased psychopathology (SCL-GSI, $\beta = .292$, $P = .058$, Figure 1C). In addition, considering the BUT subscales, hair growth (FG score) was significantly associated with

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Table 1. Summary of Estimated Means and SEs for MtF and FtM Participants by CHT Group, Including Results for Differences Tested With ANCOVA, Adjusted for All Outcome Variables

	FtMs				MtFs			
	No CHT	CHT	Adjusted D Value	Adjusted *P* Value	No CHT	CHT	Adjusted D Value	Adjusted *P* Value
SCL-90-R GSI	0.52 ± 0.44	0.48 ± 0.47	0.07 ± 0.09	.43	0.53 ± 0.05	0.45 ± 0.08	0.07 ± 0.09	.50
BUT-GSI	2.34 ± 0.09	1.80 ± 0.14	0.53 ± 0.17	**.02**	2.42 ± 0.91	1.69 ± 1.01	0.53 ± 0.17	**<.001**
BDI-II	7.17 ± 6.97	3.08 ± 3.32	4.03 ± 2.06	**.05**	9.41 ± 7.91	7.31 ± 8.55	1.86 ± 1.67	.27
GIDYQ-AA global score	2.19 ± 0.36	2.10 ± 0.27	0.11 ± 0.13	**.01**	2.28 ± 0.34	2.26 ± 0.49	0.01 ± 0.093	**<.001**
GIDYQ-subjective indicator	1.99 ± 0.35	2.20 ± 0.31	0.20 ± 0.13	.12	1.99 ± 0.41	2.29 ± 0.49	0.29 ± 0.10	**.01**
GIDYQ-social indicator	2.70 ± 0.55	2.37 ± 0.32	0.34 ± 0.19	.08	2.87 ± 0.64	2.41 ± 0.50	0.37 ± 0.13	**.01**
GIDYQ-sociolegal indicator	2.5 ± 0.90	1.56 ± 0.88	0.03 ± 0.33	**.01**	2.61 ± 1.01	2.38 ± 1.24	0.13 ± 0.25	.57
GIDYQ-somatic indicator	1.36 ± 0.7	1.14 ± 0.20	0.22 ± 0.21	.31	1.47 ± 0.71	1.57 ± 1.03	0.10 ± 0.20	.60

D, Difference.

body image avoidance (BUT-Avoidance, $\beta = .475$, $P = .001$), body image concerns (BUT-Body image concerns, $\beta = .404$, $P = .006$), and estrangement feelings toward the body (BUT-Depersonalization, $\beta = .327$, $P = .027$). When different body parts were analyzed, hair representation in lip, chin, upper abdomen, arms, and leg were positively associated with BUT-GSI ($\beta = .38$, $P = .01$; $\beta = .396$, $P = .006$; $\beta = .385$, $P = .04$; $\beta = .358$, $P = .007$; $\beta = .358$, $P = .007$, respectively). Furthermore, FG scores for chest, leg, and upper abdomen were negatively associated with subjective GIDYQ-AA ($\beta = -.375$, $P = .032$; $\beta = -.434$, $P = .007$; $\beta = -.370$, $P = .032$, respectively). When patients who had undergone augmentation mammoplasty were excluded, breast development was negatively associated

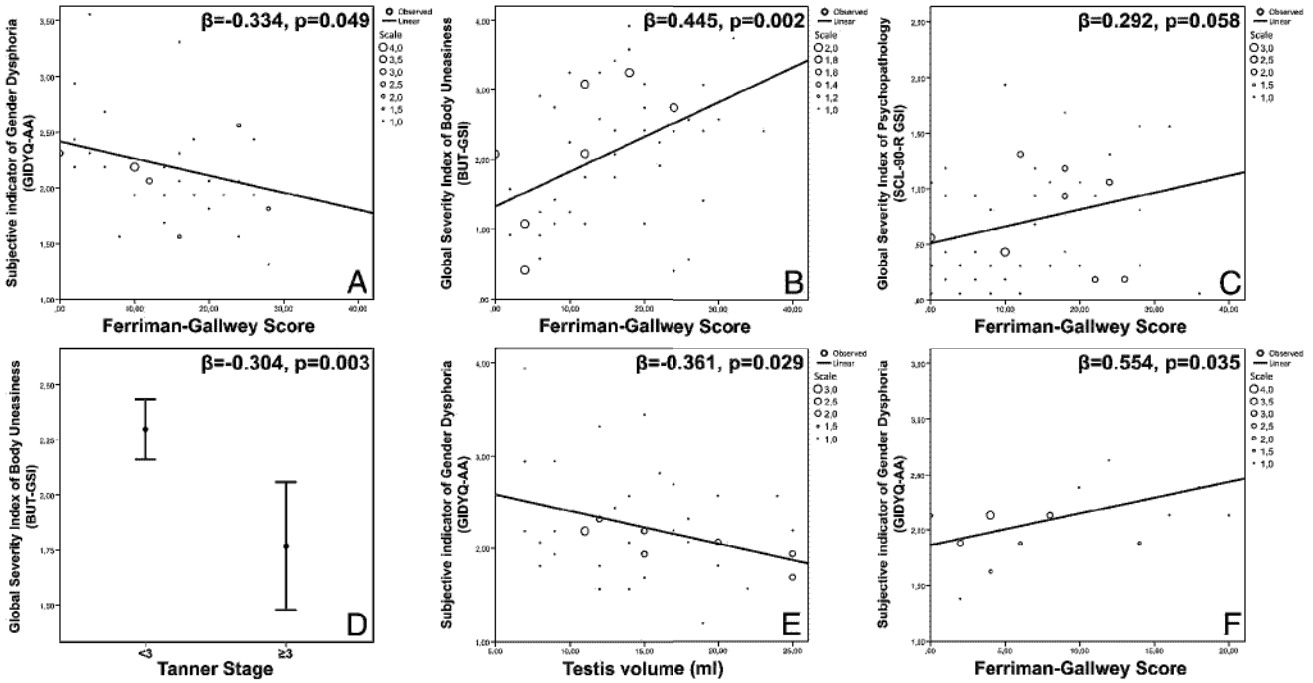

Figure 1. Associations between psychological (GIDYQ-AA, BUT-GSI, and SCL-90 R) and physical (FG score, Tanner stage, and medium testis volume) features in MtFs (panels A–E) and FtMs (panel F).

with global body uneasiness (BUT-GSI, $\beta = -.304$, $P = .003$, Figure 1D), weight phobia ($\beta = -.297$, $P = .044$), body image concerns (BUT-Body image concerns, $\beta = -.340$, $P = .017$), body avoidance (BUT-Avoidance, $\beta = -.275$, $P = .05$), and depersonalization ($\beta = -.240$, $P = .04$). Moreover, mean testis volume (Prader orchidometer) was negatively associated with a subjective GD ($\beta = -.361$, $P = .029$, Figure 1), suggesting that smaller testes are associated with lower levels of GD, as subjectively perceived. Finally, we found no correlation between T levels and testis volume ($\beta = .220$ $P = .129$),as well as between T levels and subjective GD ($\beta = -.004$, $P = .990$).

Considering FtMs, after adjustment for confounders (age, BMI, cosmetic surgery, and gender role), the FG score was associated with lower levels of subjective GD (GIDYQ-AA, $\beta = .554$, $P = .035$, Figure 1F).

Follow-up data

Psychobiological effect of CHT over time

In the sample enrolled in the longitudinal survey, average age at baseline for MtFs and FtMs resulted statistically different (t = −2.26, $P = .03$), being 32.52 ± 11.06 and 26.32 ± 7.29 years, respectively.

General psychopathology

Over time, both groups showed a significant reduction in SCL-GSI (time effect FtMs: $\beta = -.06$, $P = .01$; MtFs: $\beta = -.08$, $P = .001$), with a higher effect in MtFs (group by time interaction: F = 9.50; $P < .001$). Whereas MtFs showed a significant reduction in SCL-GSI at all time points (all $P < .01$), FtMs had a significant reduction only at T3 (t = 2.45, $P = .022$) and T4 (t = 3.40, $P = .002$) (Figure 2A).

Depressive symptoms

In addition, depressive symptoms according to BDI-II showed a significant reduction in both groups (time effect FtMs: $\beta = -1.31$, $P < .001$; MtFs: $\beta = -1.41$, $P < .001$), with a higher effect in MtFs (group by time interaction: F = 26.67; $P < .001$, Figure 2B).

Body uneasiness levels

A significant reduction of general body uneasiness was also found (time effect FtMs: b = −.24, $P = .001$; MtFs: b = −.24, $P < .001$), with a higher effect in MtFs (F = 19.70; $P < .001$, Figure 2C).

GD levels

GD levels (GIDYQ-AA) showed a significant change over time in both groups (time effect FtMs: $\beta = -.05$, $P = .001$; MtFs: $\beta = -.06$, $P < .001$, Figure 3A), without differences between them (F = 1.39; $P = .23$). In particular, GIDYQ-AA total score significantly increased at T1 and subsequently decreased at T2, T3, and T4. When GIDYQ-AA subscales were considered, a different pattern was found for subjective GD with respect to social and sociolegal ones (Figure 3, B–D). In particular, a significant decrease of subjective GD and a concurrent increase of GD related to social and sociolegal presentation were found according to months of treatment (all $P < .05$).

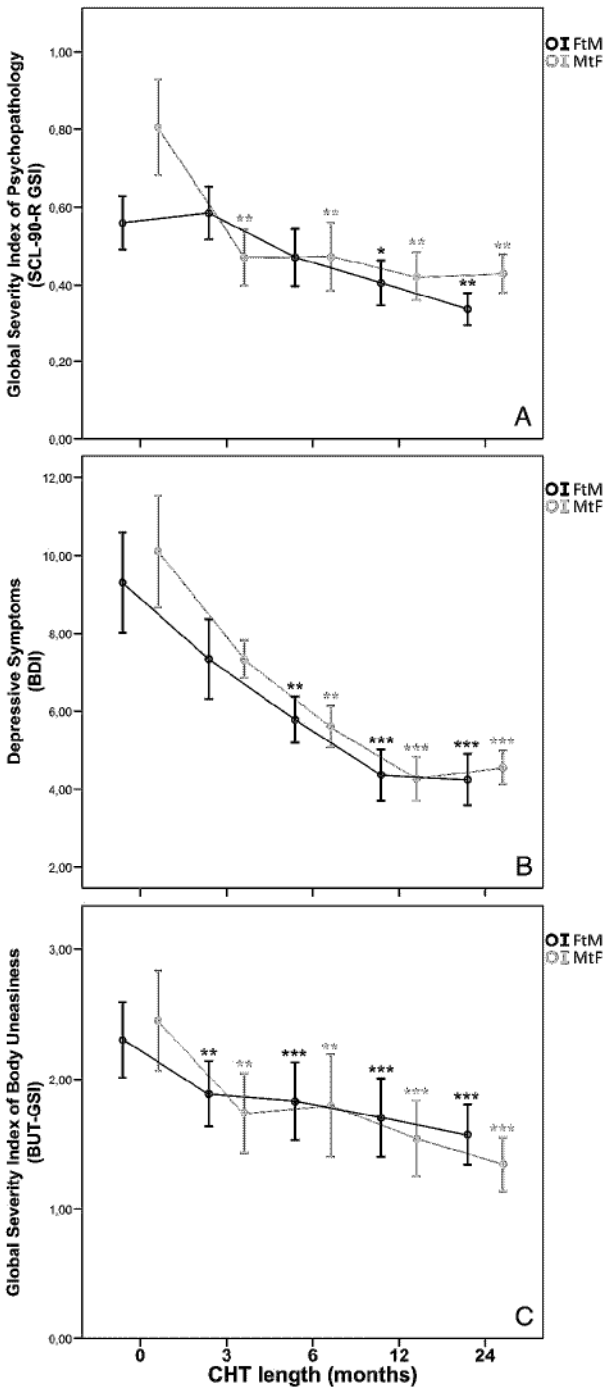

Figure 2. SCL-90 R-GSI (A), BDI (B), and BUT-GSI (C) scores at 0, 3, 6, 12, and 24 months of CHT in FtMs and MtFs (dark and gray lines, respectively). *, $P < .05$, **, $P < .01$, ***, $P < .001$ across time vs time 0 in FtM and MtF groups, respectively.

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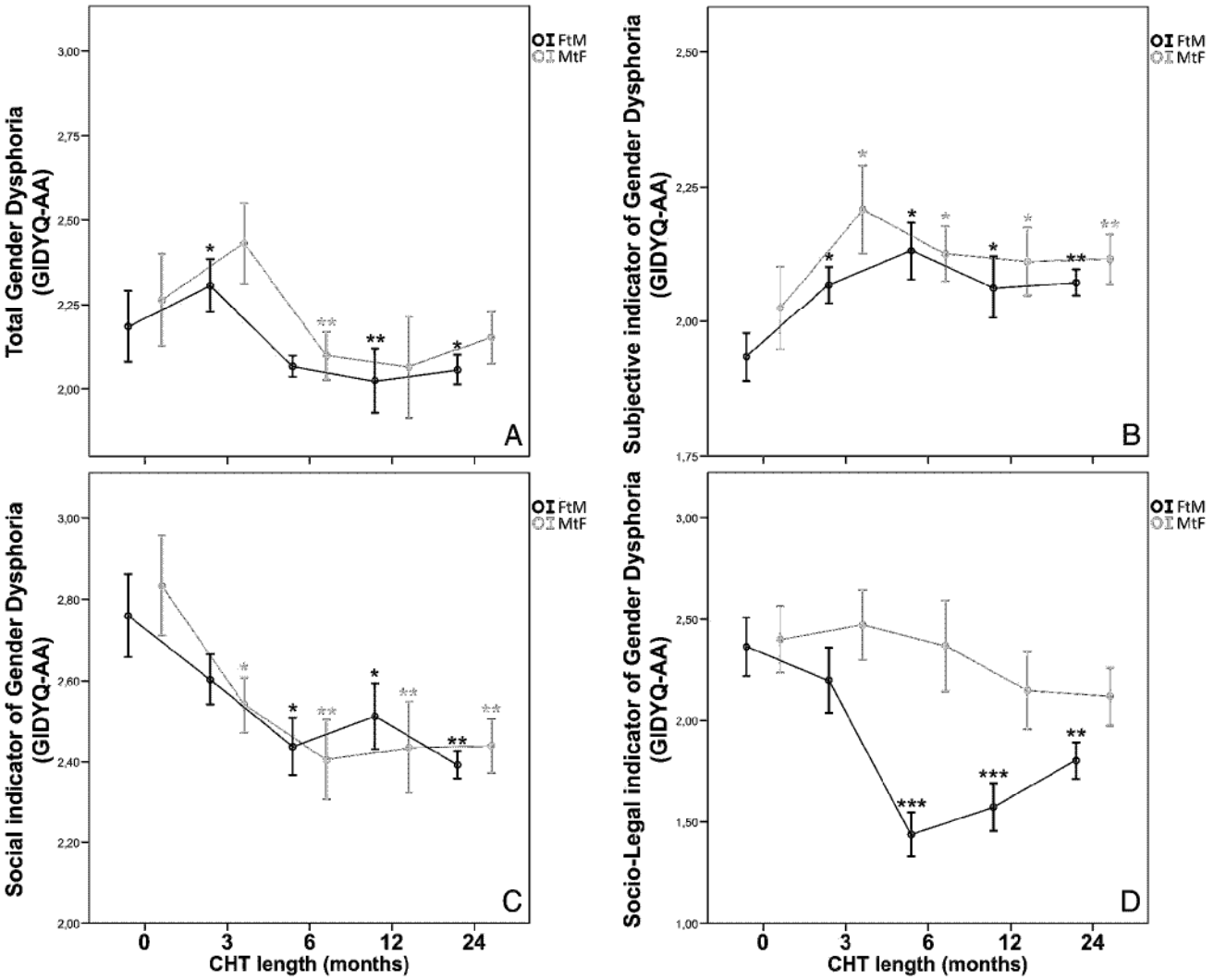

Figure 3. GIDYQ-AA total score (A), and GIDYQ-AA subjective, social, and sociolegal subscales (B–D, respectively) at 0, 3, 6, 12, and 24 months of CHT in FtMs and MtFs (dark and gray lines, respectively). *, $P < .05$, **, $P < .01$, ***, $P < .001$ across time vs time 0 in FtM and MtF groups, respectively.

Body modifications

Regarding body changes in FtMs, BMI showed a significant increase from baseline at T1 (t = −3.99, P = .001), with a further increase as a function of CHT length (all $P < .05$, Table 2), whereas waist circumference significantly increased only at T4 vs T0 (t = −3.20, P = .004). Considering genitals, clitoris length showed a marked increase from baseline at T1 (t = −9.73, $P <$ .0001), with a further, smooth increase according to CHT duration (between T0 vs T2, T0 vs T3, and T0 vs T4, all $P < .001$). Finally, the FG score showed a significant increase at T1 (t = −2.91, $P < .0001$), with further significant modification during follow-up (between T0 vs T2, T0 vs T3, and T0 vs T4, all $P < .0001$).

Considering MtFs, BMI and waist showed a significant increase as a function of CHT length (all $P < .05$, Table 2). As expected, the FG score showed a significant reduction from baseline at T1 (t = 2.55, P = .02), with a further significant modification during the following months of treatment (all $P < .0001$). In particular, a medium score lower than 8 was observed only after 24 months of CHT (t = 9.42, $P < .0001$ vs T0, see Table 2).

Regarding testis volume, we observed a significant reduction from baseline at T1 (t = 7.78, $P < .0001$), with a further significant reduction during follow-up (all $P <$ .001, Table 2). In addition, breast development showed a significant increase at T1 (F = 273.6, $P < .0001$) and a stepwise further modification according to CHT length (all $P < .0001$ at ANCOVA, Figure 4).

Impact of body changes on psychopathology over time

Males to females

In MtFs, when variations in all body parameters potentially affecting BUT (breast development, BMI, FG

Table 2. Body Changes at Baseline and 3, 6, 12, and 24 Months of CHT, Respectively, in FtMs and MtFs

	FtMs					MtFs				
	Baseline	3 Months	6 Months	12 Months	24 Months	Baseline	3 Months	6 Months	12 Months	24 Months
Waist, cm	90.97 ± 13.44[a]	90.93 ± 10.39	89.81 ± 11.40	89.97 ± 11.57	98.50 ± 10.56[b]	83.07 ± 7.84	84.00 ± 7.83	86.80 ± 7.23[b]	83.07 ± 7.85[c]	88.03 ± 5.07[b]
BMI, kg/m^2	24.88 ± 0.47[d]	25.61 ± 4.66[e]	25.84 ± 4.72[e]	25.63 ± 3.88[c]	27.72 ± 3.97[b]	21.91 ± 2.82	22.08 ± 2.48	22.45 ± 2.66[b]	22.89 ± 2.09[e]	23.02 ± 2.23[e]
Weight, kg	64.86 ± 13.86	66.68 ± 13.92[b]	66.85 ± 13.88[b]	66.85 ± 13.03[c]	75.66 ± 10.78[e]	65.26 ± 10.11	65.50 ± 9.05	67.29 ± 8.74	69.15 ± 6.69[b]	67.07 ± 4.26
FG score	4.46 ± 3.94[f]	6.92 ± 2.98[b]	13.62 ± 6.19[e]	17.65±.4.90[e]	25.46 ± 4.99[e]	16.75 ± 7.00	13.25 ± 4.66[c]	10.04 ± 3.86[e]	9.93 ± 2.76[e]	4.74 ± 2.90[e]
Medium testis volume, mL						18.06 ± 3.62	12.15 ± 0.66[e]	11.67 ± 1.63[e]	11.08 ± 1.47[e]	10.91 ± 1.05[e]
Clitoris length, cm	1.95 ± 0.62[e]	3.19 ± 0.54[e]	3.26 ± 0.60[e]	3.58 ± 0.55[e]	3.83 ± 0.42[e]					

[a] $P < .05$.

[b] $P < .01$.

[c] $P < .05$.

[d] $P < .01$.

[e] $P < .001$ across time vs time 0 in FtM and FtM groups, respectively.

[f] $P < .001$ between FtMs and MtFs.

score, testis volume) were entered as covariates in the same regression analysis model, along with the BUT score decrease, only breast development was significantly associated with a BUT reduction ($\beta = -0.405$, $P = .04$).

Females to males

When a similar model was applied to FtMs (entering as covariates clitoris length, BMI, and FG score), only the BMI increase was found to be significantly associated with a BUT decrease ($\beta = -.488$, $P = .03$).

Discussion

This is the first study simultaneously evaluating GD levels and psychopathology in transsexuals under CHT and the impact of CHT-related body changes on psychological well-being. The strength of the present study is in its multidisciplinary prospective design, evaluating both psychological and physical aspects of gender transitioning, and in the size of the population studied. Results from a cross-sectional study were also evaluated.

The main results are the following: 1) GDs under CHT reported significantly lower levels of subjective GD, body uneasiness, and depressive symptoms as compared with those without (cross-sectional study); 2) CHT-induced body modifications were significantly associated with a better psychological adjustment (cross-sectional study); 3) during CHT, patients reported a significant reduction of general psychopathology, depressive symptoms, and sub-

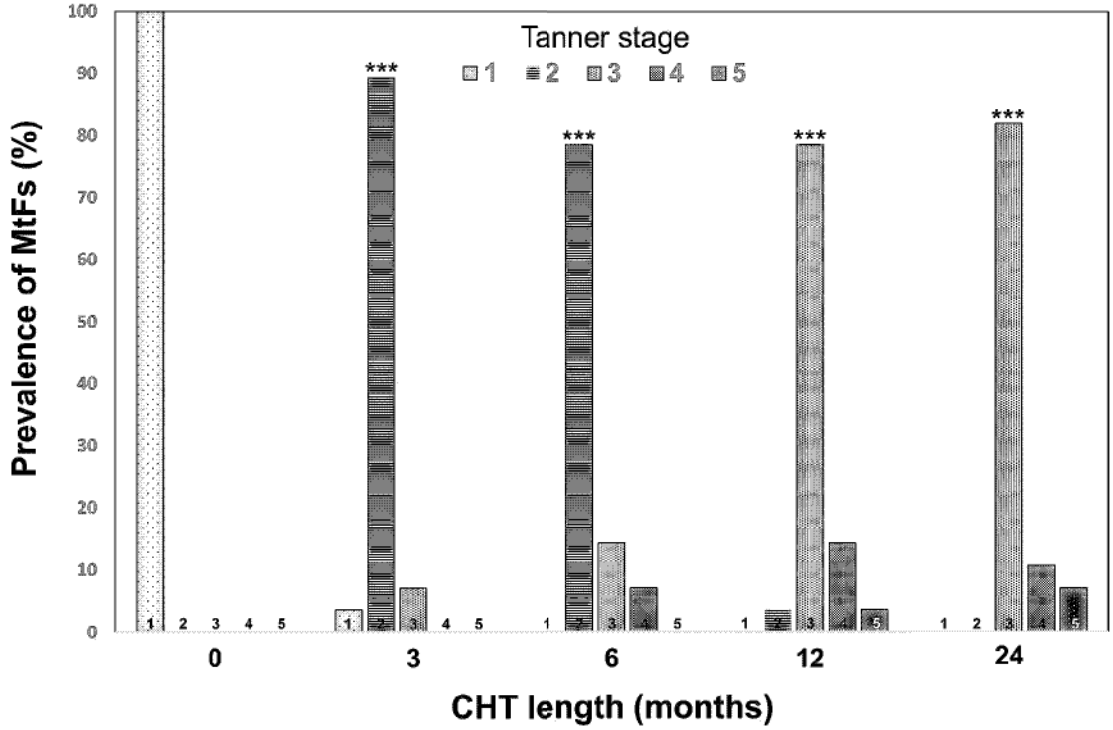

Figure 4. Percentages of MtFs with a specific Tanner stage (1–5) at 0, 3, 6, 12, and 24 months of CHT. ***, $P < .001$ across time vs time 0.

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jective GD, whereas social and sociolegal GD showed a significant increase over time (prospective study); and 4) among body changes induced by CHT, only breast development and increased BMI showed a significant impact on psychopathology reduction over time in MtFs and FtMs, respectively (prospective study).

Psychological modifications induced by CHT

Individuals under CHT alone (ie, without GRS) reported a significant reduction of subjective GD (GIDYQ-AA subjective indicator). In addition, we prospectively observed that CHT has a positive effect in alleviating body-related uneasiness (BUT). The CHT-induced concurrent improvement in both GD and body uneasiness levels highlights the centrality of body image concerns in GD development (29, 30). This is further suggested by our results from the cross-sectional sample regarding psychobiological correlates of gender-related body features.

Our results confirm that CHT is associated with a relevant improvement of general psychopathology (SCL-90-R [15, 21, 31]) and demonstrate, for the first time, a significant reduction of depressive symptoms (BDI-II) as a function of months of treatment.

The opposite trend observed during follow-up for social and sociolegal GD (GIDYQ-AA) with respect to subjective subscale can appear, at first glance, surprising. However, this conflicting result can be explained considering the sociolegal and cultural difficulties that GDs have to deal with in the Italian context.

Body modifications induced by CHT

With regard to hormonal impact on body modifications, we here evaluated the dermatological effect of CHT in a larger sample and with a longer follow-up than in previous surveys (32, 33). Our results show that 6-month T treatment was able to induce in the majority (92.7%) of FtMs an average FG score that, in women, is indicative for hirsutism (>8, 23). CHT was less effective in MtFs in obtaining the desired hair pattern (Table 2). However, the lower reliability of the FG score system should be considered in this particular population. In fact, in MtFs, hair density is often the final result of effect(s) of other hair removal systems (laser or electrolysis) in addition to CHT.

Regarding effects of CHT on body distribution, we observed in both MtFs and FtMs a significant increase of BMI and waist circumference, an indirect expression of abdominal fat distribution. These results suggest a gender-specific effect of T on fat distribution. In FtMs, T increase is associated with visceral adiposity accumulation, as observed in polycystic ovary syndrome women and in previous studies on GD (33–36) In contrast, in native males, T deficiency is associated with an increased waist circumference (37) as here observed in MtFs.

Estrogens and antiandrogens resulted in breast growth, with a significant progression over 2 years of treatment. In addition, CHT induced a marked testis volume decrease, which resulted in a 40% and 50% reduction after 1 or 2 years, respectively. This figure is higher than that previously reported by Meyer et al (38) after 1.5 years (25%) but, however, in a smaller sample and with older estrogen preparations.

Finally, in FtMs the clitoris starts to increase by 60% after only 3 months from starting T treatment and continues to grow, almost doubling after 2 years, at variance with the aforementioned study (38), demonstrating a plateau after 1 year.

Impact of body changes on psychopathology over time

Considering the psychological impact of body modifications in MtFs, only CHT-induced breast development showed a significant effect on body uneasiness decrease, whereas, surprisingly, hair distribution did not. However, it should be considered that the BUT scale is more related to the private relationship with one's own body, rather than to the distress caused by how one may appear to others (4).

Considering FtMs, CHT-induced BMI increase was the only covariate significantly associated with body uneasiness reduction. It could be speculated that in FtMs a higher BMI and waist circumference make the self-perceived body image more masculine (30) and a surrogate way to hide female shapes.

Limitations

The results of the longitudinal study should be considered as preliminary, given the small sample size, and interpreted in light of some limitations. First of all, we did not include a control, untreated group for obvious ethical reasons. However, comparisons between CHT and non-CHT subjects in the cross-sectional study support the longitudinal observations.

Another limitation is that some clinical measures were self-reported, and this could bias the results. Regarding the measures of objective body change, the subjective nature of the FG score system and breast development may lead to interobserver variability. For this reason, minimizing the number of examiners, as performed in the present study, decrease the risk of ascertainment bias, as previously suggested (23).

We did not collect ovarian morphology and polycystic ovary prevalence, due to different reasons, including uncomfortable feelings associated with transvaginal ultra-

sound and the previously reported increased incidence of polycystic ovary in FtMs (39).

Finally, hair growth in MtFs is often influenced by other cosmetic treatments (such as laser removal and electrolysis) with wide interindividual variability. However, for ethical reasons, it was not possible to ask MtFs not to use any kind of hair removal before each assessment. In addition, data regarding the extent and variety of types of hair treatment were not collected.

In conclusion, the combination of the cross-sectional and longitudinal results of the present study supports the efficacy of CHT intervention in improving the subjective perception of one's own body, which was partially associated with objective changes. Consequently, when the perceived resembles the desired body, subjective GD progressively decreases as well as the general psychopathology.

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References

1. **American Psychiatric Association.** *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Arlington, VA: American Psychiatric Publishers; 2013.
2. **Coleman E, Bockting W, Botzer M, et al.** Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgend*. 2011;13:165–232.
3. **Dèttore D, Ristori J, Antonelli P, et al.** Gender dysphoria in adolescents: the need for a shared assessment protocol and proposal of the AGIR protocol. *J Psychopathol*. 2015;21:152–158.
4. **Fisher AD, Castellini G, Bandini E, et al.** Cross-sex hormonal treatment and body uneasiness in individuals with gender dysphoria. *J Sex Med*. 2014;11:709–719.
5. **Fisher AD, Ristori J, Bandini E, et al.** Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. *J Endocrinol Invest*. 2014;37:675–687.
6. **De Cuypere G, Elaut E, Heylens G, et al.** Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *Sexologies*. 2006;15:126–133.
7. **Klein C, Gorzalka BB.** Sexual functioning in transsexuals following hormone therapy and genital surgery: a review. *J Sex Med*. 2009;6:2922–2939.
8. **Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, Birkhauser M.** Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009;92:1685–1689.e1683.
9. **Lawrence AA.** Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav*. 2003;32:299–315.
10. **Smith YL, Cohen L, Cohen-Kettenis PT.** Postoperative psychological functioning of adolescent transsexuals: a Rorschach study. *Arch Sex Behav*. 2002;31:255–261.
11. **Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT.** Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005;35:89–99.
12. **Weyers S, Elaut E, De Sutter P, et al.** Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009;6:752–760.
13. **Wierckx K, Van Caenegem E, Elaut E, et al.** Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;8:3379–3388.
14. **Bartolucci C, Gómez-Gil E, Salamero M, et al.** Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med*. 2015;12:180–188.
15. **Colizzi M, Costa R, Todarello O.** Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014;39:65–73.
16. **Leavitt F, Berger JC, Hoeppner JA, Northrop G.** Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis*. 1980;168:693–697.
17. **Newfield E, Hart S, Dibble S, Kohler L.** Female-to-male transgender quality of life. *Qual Life Res*. 2006;15:1447–1457.
18. **Murad MH, Elamin MB, Garcia MZ, et al.** Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010;72:214–231.
19. **Gorin-Lazard A, Baumstarck K, Boyer L, et al.** Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012;9:531–541.
20. **Gorin-Lazard A, Baumstarck K, Boyer L, et al.** Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013;201:996–1000.
21. **Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godas T, Cruz Almaraz M, Halperin I, Salamero M.** Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;37:662–670.
22. **Zachmann M, Prader A, Kind HP, Hafliger H, Budliger H.** Testicular volume during adolescence. Cross-sectional and longitudinal studies. *Helv Paediatr Acta*. 1974;29:61–72.
23. **Yildiz BO, Bolour S, Woods K, Moore A, Azziz R.** Visually scoring hirsutism. *Hum Reprod Update*. 2010;16:51–64.
24. **Verkauf BS, Von Thron J, O'Brien WF.** Clitoral size in normal women. *Obstet Gynecol*. 1992;80:41–44.
25. **Cuzzolaro M, Vetrone G, Marano G, Battacchi MW.** BUT, Body Uneasiness Test: a new attitudinal body image scale. *Psichiatr Infanz Adolesc*. 1999;66:417–428.
26. **Derogatis LR.** SCL-90-R: *Administration, Scoring and Procedure Manual—II*. Towson, MD: Clinical Psychometric Research; 1992.
27. **Deogracias JJ, Johnson LL, Meyer-Bahlburg HF, Kessler SJ, Schober JM, Zucker KJ.** The gender identity/gender dysphoria questionnaire for adolescents and adults. *J Sex Res*. 2007;44:370–379.
28. **Beck AT, Steer RA, Brown G.** *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corp; 1996.
29. **Bandini E, Fisher AD, Castellini G, et al.** Gender identity disorder and eating disorders: similarities and differences in terms of body uneasiness. *J Sex Med*. 2013;10:1012–1023.
30. **Jones BA, Haycraft E, Murjan S, Arcelus J.** Body dissatisfaction and

disordered eating in trans people: a systematic review of the literature. *Int Rev Psychiatry*. 2015;1–14.
31. **Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G.** Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014;11:119–126.
32. **Giltay EJ, Gooren LJ.** Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. *J Clin Endocrinol Metab*. 2000;85:2913–2921.
33. **Wierckx K, Van de Peer F, Verhaeghe E, et al.** Short- and long-term clinical skin effects of testosterone treatment in trans men. *J Sex Med*. 2014;11:222–229.
34. **Ollila MM, Piltonen T, Puukka K, et al.** Weight gain and dyslipidemia in early adulthood associate with polycystic ovary syndrome: prospective cohort study. *J Clin Endocrinol Metab*. 2016;101(2):739–747.
35. **Pelusi C, Costantino A, Martelli V, et al.** Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;11:3002–3011.
36. **Wierckx K, Van Caenegem E, Schreiner T, et al.** Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med*. 2014;11:1999–2011.
37. **Corona G, Giagulli VA, Maseroli E, et al.** Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. *Eur J Endocrinol*. 2016;174(3):R99–R116.
38. **Meyer WJ 3rd, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA.** Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav*. 1986;15:121–138.
39. **Spinder T, Spijkstra JJ, van den Tweel JG, et al.** The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab*. 1989;69:151–157.

Chest Surgery in Female to Male Transgender Individuals

Michael J. Frederick, MD, Aaron E. Berhanu, BS,† and Richard Bartlett, MD**

Background: Societal awareness of transgender individuals has led to increased acceptance and demand for sex-confirming surgery. In female to male transsexuals, the most common procedure is removal of breast tissue to masculinize the chest.

Methods: Eighty-eight transgender patients underwent either a subcutaneous nipple-sparing mastectomy (NSM) with or without a periareolar mastopexy or nipple reduction, or bilateral mastectomies with free nipple grafts (MFNG) with or without nipple reduction. Surgical techniques are discussed. Demographic data, use of testosterone, specimen weights, rates of wound dehiscence, infection, hematoma, hypertrophic scars, nipple loss, and revision surgery were all assessed.

Results: Of the 88 patients in the study, 40 underwent NSM and 48 underwent MFNG. Patients undergoing NSM were 4.1 times more likely to have a hematoma compared with patients undergoing MFNG ($P < 0.05$). Mastectomy weight was not correlated with the occurrence of hematoma ($P > 0.80$). Only 1 patient who underwent NSM required revision, whereas 5 patients in the MFNG patient population underwent revision. Patients were more likely to have hypertrophic scarring with the MFNG technique (0% vs 25%, $P < 0.01$) There were no infections, no wound dehiscence, and no nipple loss in any patient. Eighty-three percent of the patients who responded to a satisfaction survey (57/88) were very satisfied with their result, and 100% would recommend this procedure to other transgender individuals.

Conclusions: Female to male transgender mastectomy can be performed with low complication rates and high satisfaction. Nipple-sparing mastectomy were more likely to have a hematoma than patients undergoing MFNG.

Key Words: transgender, top surgery, transsexual, breast

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Awareness of transgender individuals in the wider society has led to increased acceptance and demand for surgical services. In female to male transsexuals, the most common procedure is removal of breast tissue to masculinize the chest.[1]

Estimates of the number of female to male transsexuals have increased steadily. In 1968, Pauly[2] estimated that the prevalence of female to male transgender individuals was at minimum 1:100,000. The incidence of transgender female to male individuals has since been estimated to be from 1:30,400 to as high as 1:8300.[3] Surveys through various departments of public health suggest that 0.1% to 0.5% of the population has taken steps to transition from 1 gender to another.[4,5] With increased acceptance of transgender individuals, there has been an increased awareness of the medical needs of this population. The 2 major sex reassignment surgeries are subcutaneous mastectomy and genital reconstruction. The first and most common procedure requested is surgery to masculinize the chest.[1]

Commonly referred to as "top surgery," masculinization requires removal of breast tissue. Although the procedures are similar to traditional gynecomastia techniques, they differ in the extent of breast excision. Transgender patients have more extensive breast development with a well-defined axillary tail of Spence. A wider dissection is necessary to remove all glandular tissue. The goal is to eliminate residual hormonal effects on the breast and to obviate the need for breast screening.

However, the surgery involves more than a simple mastectomy as described for the treatment of breast cancer. The aesthetic requirements to achieve an acceptable male appearance have been described by Hage and van Kesteren[6] and include chest wall contouring, reduction, and proper positioning of the nipple areolar complex (NAC), and minimizing scars. Multiple authors have reviewed the spectrum of procedures from subcutaneous mastectomy to mastectomies with free nipple grafts. Monstrey et al[7] described an algorithm that based surgical decision-making on breast size, degree of ptosis, and skin elasticity with a progressively aggressive skin resection and subsequent increase in visible scarring as each parameter became less ideal.

The principles elucidated by these and other authors remain valid. However, with the advent of social media, we have found that patients present to the office well informed, often having watched the surgery online and discussed the experience in a community of individuals who have taken steps to transition their sex. Such patients expect to have an increased role in the decision-making process and often present with requests for specific surgical procedures. In this article, we present our 6-year experience with female to male chest surgery and describe our process for surgical decision making.

METHODS

From December of 2008 to March of 2014, 88 transgender female to male patients underwent surgery to masculinize their chest. Patient intake was via consultation with review of medical records and psychological history. The World Professional Association for Transgender Health Standards of Care, were used to screen patients regarding suitability for surgery.[8] World Professional Association for Transgender Health Standards of Care require that the patient display persistent, well-documented sex dysphoria and live in their new sex role at all times and all settings for 1 year. Patients must also show the capacity to make a fully informed decision. If significant medical or mental health concerns are present, they must be reasonably well controlled. A letter from a licensed therapist is also required. Based on physical examination and discussion with the patient, 2 basic procedures were performed, either a subcutaneous nipple sparing mastectomy with or without a periareolar mastopexy and nipple reduction, or bilateral mastectomies with free nipple grafts with or without nipple reduction.

Follow-up occurred at 1 week, 3 weeks, 3 months, and 1 year. In cases where the patients lived a considerable distance from Boston, long-term follow-up was conducted by email communication. Patients were contacted for satisfaction surveys by email, telephone, and direct mail. The questionnaire is depicted in Figure 1. Statistical analyses of results were performed with *t* tests and Fisher exact tests.

Operative Techniques

All surgeries were performed under general anesthesia on an outpatient basis. Patients were instructed to shower with a chlorhexidine topical solution for 2 days before surgery.

Nipple-sparing mastectomy (NSM) was performed through a semicircular infra-areolar approach. Dissection was carried out using the electrocautery on cutting mode as well as sharp dissection. Care was taken to leave all subcutaneous tissue intact on the skin flaps to minimize co[illegible] the breast

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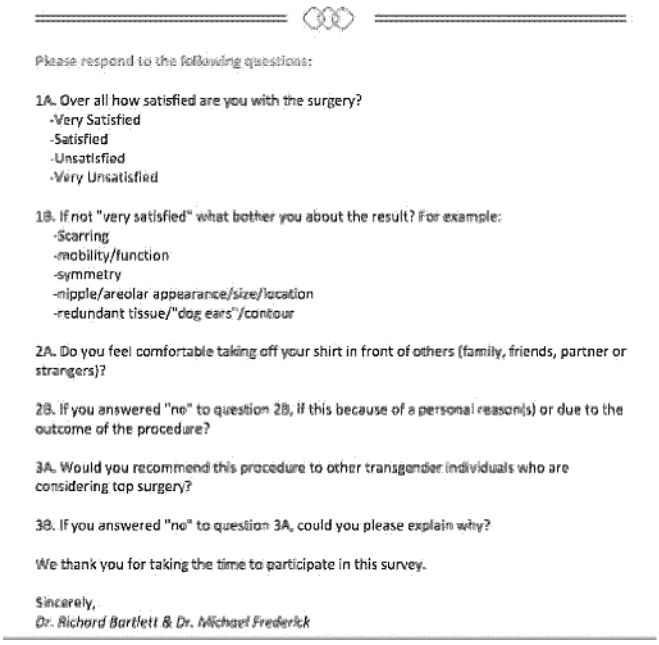

Please respond to the following questions:

1A. Over all how satisfied are you with the surgery?
-Very Satisfied
-Satisfied
-Unsatisfied
-Very Unsatisfied

1B. If not "very satisfied" what bother you about the result? For example:
-Scarring
-mobility/function
-symmetry
-nipple/areolar appearance/size/location
-redundant tissue/"dog ears"/contour

2A. Do you feel comfortable taking off your shirt in front of others (family, friends, partner or strangers)?

2B. If you answered "no" to question 2B, if this because of a personal reason(s) or due to the outcome of the procedure?

3A. Would you recommend this procedure to other transgender individuals who are considering top surgery?

3B. If you answered "no" to question 3A, could you please explain why?

We thank you for taking the time to participate in this survey.

Sincerely,
Dr. Richard Bartlett & Dr. Michael Frederick

FIGURE 1. Patient satisfaction survey instrument.

contour, the dissection was continued under the breast with effort being made to avoid violating the pectoralis fascia. Occasionally, the specimen had to be delivered in segments due to the limited aperture of the infra-areolar incision. After hemostasis was obtained, the incision was closed in layers using 5-0 poligecaprone 25, an absorbable monofilament suture. In cases where an areolar reduction was indicated, a new areola dimension of 25 mm was marked and the periphery was deepithelialized in a very superficial plane before the mastectomy. In cases where the discrepancy between the outer and inner circumferences was 2 cm or greater, placement of a deep dermal Benelli-type suture of 3-0 polyester was considered. Nipple reduction was by central resection and creation of 4 triangular flaps and was also done before the mastectomy. Round Jackson Pratt drains, no. 10 or no. 15, were placed before closure.

Mastectomies and free nipple grafts (MFNG) were begun by marking the patient in the preoperative waiting area to optimize scar and nipple placement. After initiation of anesthesia, the areolas were marked at a 22-mm diameter. If the nipples had significant projection, a nipple reduction was performed, and the areolas were harvested and stored in saline. Elliptical incisions were made around the base of each breast and simple mastectomies were carried out. The resulting scar was intended to lie at the caudal border of the pectoralis muscle, not necessarily the inframammary fold (IMF). Undermining was carried below the IMF, and the fascia was released if necessary to obliterate the IMF. Uniform skin flap thickness was maintained and minimal subcutaneous fat was excised. Number 15 Jackson Pratt drains were placed through lateral stab incisions. After closure of the mastectomy sites, the new areola locations were chosen with the patient in a sitting position and were de-epithelialized. The areolas were thinned manually and inset using half buried horizontal mattress sutures of 4-0 and 5-0 plain gut. Tie-over bolsters were constructed from Xeroform, cotton, and mineral oil.

For both NSM and MFNG, Marcaine 0.25% was infiltrated diffusely before wound closure. A compression garment was left on for at least 1 week. Drains and bolsters were usually removed at the 1-week postoperative visit. Patients were instructed to take off at least 1 week from work and exercise was prohibited for 6 weeks postoperatively. The MFNG graft patients or anyone with a history of hypertrophic scarring were instructed to use silicone sheeting for 12 hours a day beginning at postoperative week 6.

RESULTS

The median age of the 88 patients in the study was 24 years, with a range of 15 to 71 years. The median BMI was 22.3, with a range of 18.6 to 41.3. Exogenous testosterone was used by a majority of the patients preoperatively (65/88 = 74%). Four patients had previously undergone a breast reduction, and 2 had undergone a hysterectomy.

A majority of the cohort underwent MFNG (48/88 = 54.5%) and the remaining underwent NSM (Table 1). The median total breast tissue excised per patient was 493.5 g (Table 1).

There were 8 short-term (<30 days) complications, all of which were hematomas. There were no surgical site infections, wound dehiscence, or loss of the NAC. Patients undergoing NSM were 4.1 times more likely to have a hematoma compared with patients undergoing MFNG ($P < 0.05$). All instances of hematoma occurred in patients on testosterone therapy. The coincidence of hematoma formation and testosterone use was statistically significant ($P < 0.05$). Mastectomy weight was not correlated with hematoma formation ($P > 0.80$).

There were 21 long-term complications, including 9 dog ears and 12 hypertrophic scars (Table 2). Although the majority of dog ears occurred in the MFNG group, statistical significance was not demonstrated in comparison to the NSM group ($P > 0.05$). All 12 of the patients who developed hypertrophic scars underwent MFNG. The coincidence of hypertrophic scar formation and MFNG was statistically significant ($P < 0.05$). The development of a long-term complication does not appear to affect overall patient satisfaction (Table 2).

There were 7 revision procedures performed in 6 patients (6.8% of 88 patients). Two patients underwent hypertrophic scar removal, 3 patients had a dog ear revision, and 1 patient received both a dog ear revision and a nipple reduction.

Patient satisfaction was assessed in 57 patients (64.8% of 88 patients) (Table 3). The remaining 31 patients could not be reached via email, telephone, or direct mail for completion of the survey. A majority of survey respondents were "very satisfied" with the results of their surgery (47/57 = 82.5%). An additional 9 respondents (15.8%) were "satisfied" and 1 patient (1.8%) was "very unsatisfied" with the results of their surgeries. The 5 qualitative responses for overall satisfaction with the results of surgery were converted to a quantitative scale from 1 to 5, with 1 representing "very dissatisfied" and 5 representing "very satisfied." Using this quantitative scale, the mean satisfaction of the entire cohort was 4.77 (Table 3). The mean satisfaction for the NSM group was 4.76, and satisfaction in the MFNG group was slightly

TABLE 1. Frequency of Surgical Procedures and Excision Weight

		Patients	Median Excision *g* (Range)
NSM	Only	10	303.5 (210–507)*
	NR	5	247 (98–319)
	AR	10	287 (202.5–460)†
	AR + NR	15	219 (130–480)*
		40 (45.5%)	266 (98–507)
MFNG	Only	47	1007.5 (362–2760)
	NR	1	1118
		48 (54.5%)	1055 (362–2760)
	Σ	88	493.5 (98–2760)

*Weight not recorded for 2 patients.
†Weight not recorded for 1 patient.
AR, areolar reduction; NR, nipple reduction.

TABLE 2. Frequency of Complications and Resulting Satisfaction Scores

Complication	Frequency	Original Procedure	Management	Satisfaction Score Average
Short-term				
Hematoma	8	NSM only = 2 NSM + NR = 1 NSM + AR = 2 NSM + AR + NR = 1 MFNG only = 2	8, surgical evacuation	5
Infection	0			
Dehiscence	0			
NAC loss	0			
Long-term				
Axillary dog ear	9 (10.2%)	MFNG only = 7 NSM + AR = 1	3, surgical excision	4.75
Hypertrophic scar	12 (13.6%)	MFNG only = 12	1, surgical scar revision	4.78

higher at 4.78, but this difference was not found to be statistically significant ($P > 0.05$). Of the patients reporting that they were "satisfied," concerns were nipple appearance (2), scar (2), and contour irregularities (3). For the 1 patient who reported he was "very unsatisfied," concerns included scar and contour irregularities.

Most patients (48/57 = 84.2%) indicated that they feel comfortable taking their shirt off in front others, which included some combination of a partner, family, friend, or strangers. All survey respondents would recommend a mastectomy procedure to other transgender individuals.

DISCUSSION

Selecting the appropriate surgical technique is the most important factor in optimizing aesthetic results and minimizing the need for significant secondary surgery. The difference in specimen weight between the 2 techniques (Table 1) reflects the fact that much larger breasts are being removed in the MFNG group. There are a range of weights that overlap in the 2 groups, indicating that factors other than size are taken into account when deciding on procedure. In general, smaller breasts with elastic skin are amenable to a periareolar approach (Fig. 2), and larger breasts require a mastectomy with a free nipple graft (Fig. 3). There is however a group of patients who do not have large breasts but exhibit grade 1 or grade 2 ptosis or have significant skin laxity (Fig. 4). Many of these individuals present requesting NSM because of the relatively short and inconspicuous scar. Such individuals are not ideal candidates for a procedure that relies on significant skin contracture but may wish to proceed anyway. These patients should be counseled regarding the risk of inadequate skin contracture and the possibility of significant contour irregularities. They should be informed that significant secondary surgery with increased scarring, added expense, and a new recovery period may be necessary.

Ptotic breasts with redundant inelastic skin require a mastectomy and a free nipple graft. Although the technique results in a much more conspicuous scar, careful positioning of the scar and the nipple areola complex can improve the result. Techniques have been described using scars that extend tangentially from the NAC.[7] We feel that a scar across the center of the breast is unaesthetic. Scars which lie increases are less noticeable and for that reason, we place the scar at the caudal border of the pectoralis muscle. This landmark is not necessarily at the level of the existing inframammary crease in large breasts. If necessary, the caudal mark for the elliptical incision is moved up on the breast so that the resulting scar rests cephalad to the IMF. Fascia is disrupted as needed to blur the IMF crease. Because of the difficulties in draping redundant skin, the chance of producing a "dog ear" of redundant tissue is higher in patients with a MFNG technique. Lateral dog ears are excised at the initial procedure when obvious. Medial dog ears often necessitate connecting the 2 incisions of the "double incision" procedure across the midline. Despite these efforts, the incidence of revision was 10% in MFNG patients, 75% of which were dog ears excisions, similar to the other published results.[6,7]

Areola size and location also affect outcome. Between the NSM group and the MFNG group, 89% of patients required resizing of the areola. Multiple studies have found that the "ideal" male areola is approximately 25 mm.[9,10] In the NSM/periareolar mastopexy group, a new dimension of 25 mm was used. In the MFNG group, there appears to be some stretching of the areola, possibly due to tension on the skin closure or slight hypertrophy of the periarolar scar. After this phenomenon was noticed, a dimension of 22 mm was used for free nipple graft dimensions to allow for slight expansion during wound healing. Nipple location was not altered in the NSM group, even in the instance where a periareolar mastopexy was performed. For patients having MFNG, the new areola site was placed in accordance with previously published guidelines[9,10] in the fourth to fifth interspace and approximately 11 cm from the sternal midline. Our own findings indicate that the areola is often 1.5 cm above our chosen infrapectoral scar. Because it is difficult to site the areola preoperatively with a large breast and the fact that intraopertively tension is placed on the skin which may alter the position of previously placed marks in an unpredictable way, a grid is marked on the patient's chest (Fig. 5). Vertical lines are at 5 and

TABLE 3. Satisfaction Scores by Procedure

		Completed	Response Rate	Satisfaction Score Average
NSM	Only	4	40.0%	4.75
	NR	4	80.0%	4.75
	AR	6	60.0%	4.67
	AR + NR	11	73.3%	4.82
			62.5%	4.76
MFNG	Only	31	66.0%	4.77
	NR	1	100.0%	5.00
			66.7%	4.78
All	Σ	57	64.8%	4.77

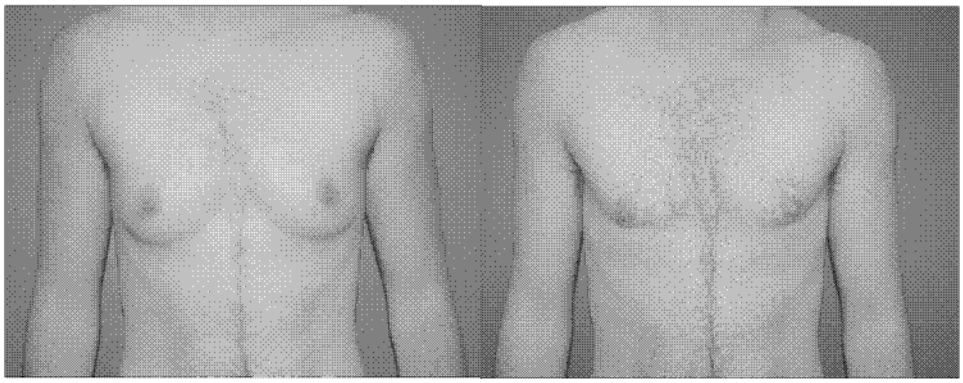

FIGURE 2. (Left) A 24-year-old patient on testosterone for 2 years. The patient has small breasts and good skin elasticity with an areola diameter of 35 mm on stretch. (Right) The 6-month postoperative view after bilateral nipple sparing mastectomies and a periareolar mastopexy. The new areola diameter is 22 mm.

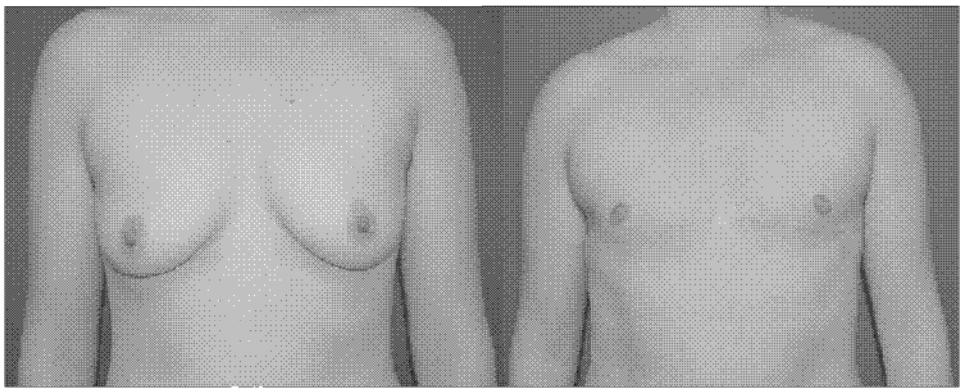

FIGURE 3. (Left) Preoperative view of a 25-year-old patient with glandular ptosis and moderate skin laxity. The patient is not on testosterone. (Right) One-year postoperative view after bilateral mastectomies, free nipple grafts and nipple reduction. The patient underwent revision of a hypertrophic scar on the medial left infrapectoral incision line at 6 months.

10 cm from midsternum and horizontal lines are placed at 10, 12, and 14 cm from the clavicle. The lateral border of the pectoralis is also marked. After closure of the infrapectoral incision, the patient is placed into a sitting position, and the new areola sites are confirmed and marked. The previously marked grid allows for improved orientation and symmetrical outcomes.

The final component of NAC construction is adjustment of nipple size. Most MFNG patients will lose enough nipple projection through defatting of the areola that actual external reduction of the nipple will not be necessary. Early in our series, nipples were more aggressively reduced in MFNG patients with the result that nipple projection was lost altogether. In the NSM group, overprojecting nipples will not shrink without active intervention. In such patients, a 4-flap nipple reduction at the time of NSM with or without periarolar mastopexy is offered. No nipples were lost regardless of technique, but 12.5% (1 of 8) of the revisions and 50% of the patients (2 of 4) with a complaint about their surgery were related to an oversized nipple.

Complications with transgender mastectomy are rare. Similar to other studies, hematoma was the most common short-term complication and occurred more often in patients undergoing an NSM.[6,11] This is likely due to decreased visualization while obtaining hemostasis during the operation given the small periareolar incision. Although testosterone use did correlate with hematoma formation, it is unclear whether this caused their increased incidence, because hormone treatments are known to be prothrombotic. Other studies have not shown any correlation between testosterone use and hematoma formation or thrombotic complications.[11] There were no episodes of nipple necrosis, even in the hematoma group.

The most common long-term complication is a hypertrophic scar, which only occurred in the patients with MFNG technique. All late revisions were related to revision of hypertrophic scars or dog ear

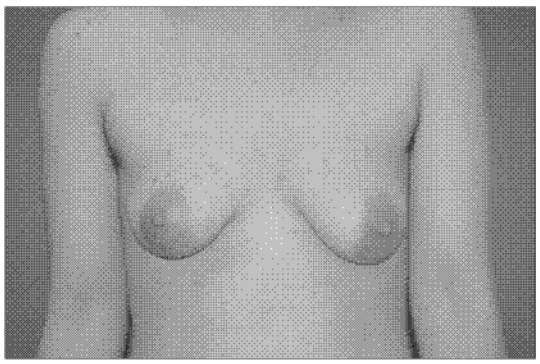

FIGURE 4. Nonideal candidate for a short incision technique. Such patients often present believing that they are candidates for a nipple sparing mastectomy because they have small breasts. Such patients require counseling regarding the inability of their skin to contract sufficiently and the possibility of significant contour irregularities.

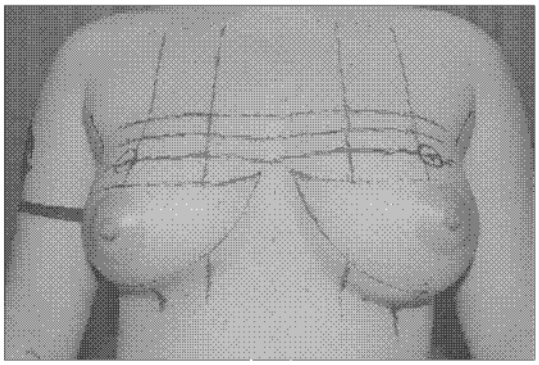

FIGURE 5. Preoperative marking for mastectomies and free nipple grafts showing the orientation grid and proposed new sites for the NAC. Note that the caudal incision line is drawn above the inframammary crease so that the final scar will lie near the pectoral insertion.

excision. Incisions directly on the chest as opposed to the breast are known to have higher rates of hypertrophic scarring and these can be treated with re-excision, silicone sheeting, steroid injection or laser treatment as is appropriate.[12] All late revisions were related to revision of hypertrophic scars or dog ear excision. The incidence of revision was 10% in MFNG patients, 75% of which were dog ear excisions, similar to other published results.[6,7] Such revisions are minor, require only local anesthesia, do not require a prolonged recovery, and do not impact patient satisfaction.

There is no validated method of assessing transgender surgery outcomes, because this population presents problems for follow-up. These surgeries are relatively uncommon, the patients often travel long distances for their operation, patients often move and change identity, and transgender patients are particularly concerned with maintaining confidentiality.[3,11] Despite these challenges, several studies have tried to categorize outcomes by an analog scale and have had similar results to ours showing that most people are very satisfied with their outcome.[11] However, these metrics are not sufficient and do not examine how the patient is integrating into their new life. Transgender and nontransgender cosmetic patients have similar preoperative feelings toward their bodies, similar cosmetic and psychological motivations for surgery, and similar benefits of surgery.[13] In our patient population, 84.2% felt comfortable taking their shirt off in front of others, and 100% would recommend the surgery to other transgender individuals. Although we are pleased with these outcomes, we recognize that a more in depth and validated procedure-specific survey, such as the Breast-Q, would be more optimal to measure patient-reported outcomes.[14]

CONCLUSIONS

Awareness of transgender individuals has led to increased acceptance and demand for surgical services. Female to male transgender mastectomy can be performed with low complication rates with high patient satisfaction.

REFERENCES

1. Monstrey SJ, Ceulemans P, Hoebeke P. Sex reassignment surgery in the female-to-male transsexual. *Semin Plast Surg*. 2011;25:229–244.
2. Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968;147:460–471.
3. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478–484.
4. Olyslager F, Conway L. *On the Calculation of the Prevalence of Transsexualism*. Chicago, Illinois: Paper presented at the WPATH 20th International Symposium; 2007.
5. Reed B, Rhodes S, Schofield P, et al. *Gender Variance in the UK: Prevalence, Incidence, Growth, and Geographic Distribution*. Gender Identity Research and Education Society; 2009.
6. Hage JJ, van Kesteren PJ. Chest-wall contouring in female-to-male transsexuals: basic considerations and review of the literature. *Plast Reconstr Surg*. 1995;96:386–391.
7. Monstrey S, Selvaggi G, Ceulemans P, et al. Chest-wall contouring surgery in female-to-male transsexuals: a new algorithm. *Plast Reconstr Surg*. 2008;121:849–859.
8. World Professional Association for Transgender Health Standards of Care, Version 7, 2012.
9. Shulman O, Badani E, Wolf Y, et al. Appropriate location of the nipple-areola complex in males. *Plast Reconstr Surg*. 2001;108:348–351.
10. Beckenstein MS, Windle BH, Stroup RT. Anatomical parameters for nipple position and areolar diameter in males. *Ann Plast Surg*. 1996;36:33–36.
11. Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg*. 2012;65:711–719.
12. Wolfram D, Tzankov A, Pülzl P, et al. Hypertrophic scars and keloids—a review of their pathophysiology, risk factors, and therapeutic management. *Dermatol Surg*. 2009;35:171–181.
13. Windsor EJ. *Regulating Healthy Gender: Surgical Body Modification among Transgender and Cisgender Consumers*. Dissertation, Georgia State University; 2011.
14. Pusic AL, Klassen AF, Scott AM, et al. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg*. 2009;124:354.

Off-Label Use of Drugs in Children

Article *in* PEDIATRICS · March 2014

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Off-Label Use of Drugs in Children

COMMITTEE ON DRUGS

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POLICY STATEMENT

Off-Label Use of Drugs in Children

COMMITTEE ON DRUGS

KEY WORDS
off-label drug use, pharmaceuticals, pediatrics, infants, children, adolescents, prescribing

ABBREVIATIONS
BPCA—Best Pharmaceuticals for Children Act
FDA—US Food and Drug Administration
PREA—Pediatric Research Equity Act

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abstract

FREE

The passage of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act has collectively resulted in an improvement in rational prescribing for children, including more than 500 labeling changes. However, off-label drug use remains an important public health issue for infants, children, and adolescents, because an overwhelming number of drugs still have no information in the labeling for use in pediatrics. The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient. *Pediatrics* 2014;133:563–567

INTRODUCTION

The purpose of this statement is to further define and discuss the status of off-label use of medications in children. Since publication of the 2002 statement from the American Academy of Pediatrics on the off-label use of drugs,[1] the number of drugs approved by the US Food and Drug Administration (FDA) with pediatric indications or expanded labeling that informs drug use in pediatric patients (eg, pharmacokinetic/pharmacodynamic data, safety data) has substantially increased. The passage of the Best Pharmaceuticals for Children Act[2] (BPCA) and the Pediatric Research Equity Act[3] (PREA) has resulted in more than 500 pediatric labeling changes. However, despite this success and advances in both basic science and clinical trials in pediatrics, off-label drug use remains a common and important issue for children and adolescents. Moreover, off-label use of drugs presents an even larger and more complex issue in preterm and full-term neonates, infants and in children younger than 2 years,[4] and children with chronic and/or rare diseases.

DEFINING OFF-LABEL USE

The term "off-label" use refers to use of a drug that is not included in the package insert (approved labeling) for that drug. The purpose of off-label use is to benefit an individual patient. It is important to note that the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use. To approve a drug for sale and marketing within the United States, the FDA requires substantial

evidence for efficacy and safety, usually in the form of 2 well-controlled trials. Subsequent requests by a sponsor to add a new indication to drug labeling must also be accompanied by additional evidence in support of that indication. If the FDA finds that such evidence supports approval, the new indication is added to the product labeling. If the evidence is deemed insufficient or if the sponsor chooses not to submit evidence, the indication is not added.

According to the Code of Federal Regulations,[5] a sponsor is the entity that holds an investigational new drug application and that both takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. A sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual who uses 1 or more of his or her own employees to conduct an investigation that he or she has initiated is considered to be a sponsor, not a sponsor-investigator. In this case, the employees are investigators. Sponsor-investigators both initiate and conduct an investigation and direct the administration or dispensing of the investigational drug. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor. It is important to note that sponsors are not allowed to promote or even speak to off-label use. If a physician speaks on behalf of a sponsor, the same rule applies. It is acceptable to use drugs off label and to publish results related to off-label use, but it is not acceptable to receive remuneration from the sponsor for these uses.

The absence of labeling for a specific age group or for a specific disorder does not necessarily mean that the drug's use is improper for that age or disorder. Rather, it only means that the evidence required by law to allow inclusion in the label has not been approved by the FDA. Additionally, in no way does a lack of labeling signify that therapy is unsupported by clinical experience or data in children. Instead, it specifically means that evidence for drug efficacy and safety in the pediatric population has not been submitted to FDA for review or has not met the regulatory standards of "substantial evidence" for FDA approval. In contrast to the absence of pediatric-specific information on some medications, other drug labels contain statements such as "the safety and efficacy in pediatric patients have not been established," and explicit evidence-based warnings and contraindications are included on the label where indicated. Understanding the distinction between the lack of FDA approval for a particular use or dosing regimen in the former case versus explicit warnings or contraindications against use in the latter is essential for the pediatric practitioner. In addition, when considering best practices for therapeutic decision-making, it is essential to understand that the FDA does not regulate the use of drugs as they pertain to the practice of medicine.[6]

THE ROLE OF THE FDA

The FDA is the federal government agency charged with oversight responsibility for the manufacturing, labeling, advertisement, and safety of therapeutic drugs and biological products. The Food, Drug, and Cosmetic Act[7] requires that "substantial evidence," resulting from "adequate and well-controlled investigations" demonstrating that a new drug "will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling," be submitted to and reviewed and approved by the FDA before the drug is marketed in interstate commerce. For drugs and biological agents (eg, vaccines, antibodies), proof of effectiveness consists of "adequate and well-controlled studies" as defined for new drugs in the Code of Federal Regulations.[8] Biological agents are approved under the Public Health Service Act.[9] Given these requirements as well as the rapid pace of medical discovery, it is not surprising that labeling does not reflect all possible uses of an agent. Off-label use of drugs in children is not overseen by the FDA, because the FDA does not regulate the prescription practices of individual practitioners.

The FDA maintains a system for postmarketing drug surveillance, compiling and analyzing information about the incidence and severity of adverse events reported by practitioners, sponsors, hospitals, and other health care facilities. It is important to note that this postmarket surveillance system is passive and that the total number of adverse event reports in pediatrics relative to adults is small. To address this issue, the BPCA provides for a systematized review of adverse event reports in pediatric patients through the FDA Pediatric Advisory Committee. When the FDA notes an apparent association between use of a drug and an adverse event, the FDA may choose from several actions: to request further focused study of the drug, to add a contraindication or warning to the drug labeling, to issue a warning about use of the drug, or to seek voluntary or compulsory removal of the drug from the market. Therefore, although the FDA does not regulate the practice of medicine, practitioners should be aware of new information brought forward by the FDA, because it can serve as a valuable resource for information regarding the potential or proven adverse effects of drugs (see www.fda.gov).

THERAPEUTIC DECISION-MAKING

Therapeutic decision-making should always be guided by the best available evidence and the importance of the benefit for the individual patient. Practitioners are in agreement regarding the importance of practicing evidence-based medicine. However, for the pediatric population, gold standard clinical trials are often not available, so practitioners must rely on either less definitive information, such as expert opinion for the age group that they are treating, or use evidence from a different population to guide practice. There are now many resources available to help assess the quality of evidence-based medicine, including but not restricted to articles in peer-reviewed journals, American Academy of Pediatrics practice guidelines and policy statements, consensus statements, and handbooks and databases (ie, Cochrane, Lexicomp, and Harriet Lane). At times, there may be little or no published information to guide therapy. This situation is especially true when treating rare diseases or sparse populations such as neonates. In such situations, the practicing physician can play an important role in adding to therapeutic information by publishing his or her experience with off-label uses of drugs. These reports can serve as the basis of more formal efficacy and safety studies and can serve as a therapeutic decision-making resource for other physicians. The practicing physician also has a responsibility to report adverse events to the FDA through the Medwatch program (www.fda.gov/Safety/MedWatch).

In most situations, off-label use of medications is neither experimentation nor research. The administration of an approved drug for a use that is not approved by the FDA is not considered research and does not warrant special consent or review if it is deemed to be in the individual patient's best interest.[6]

In general, if existing evidence supports the use of a drug for a specific indication in a particular patient, the usual informed-consent conversations should be conducted, including anticipated risks, benefits, and alternatives. If the off-label use is based on sound medical evidence, no additional informed consent beyond that routinely used in therapeutic decision-making is needed.[10] However, if the off-label use is experimental, then the patient (or parent) should be informed of its experimental status.[11] It would be prudent for pediatricians to know and abide by the appropriate informed consent laws in their respective states. In addition, particular risk-benefit ratios presented by the unproven therapies must be carefully considered and disclosed, and standard of care practices should be reviewed. When use of a drug is truly investigational, drug use should be performed in conjunction with a well-designed clinical trial whenever possible. This is especially true when the physician proposes to treat a group of patients rather than a single individual. Patients and/or their legal guardians should be specifically informed that the proposed therapy is investigational, and their consent to proceed despite the risks of investigational therapy should be carefully documented. Whether institutional review, consultation, or written consent are required for a given intervention depends on the degree of risk or departure from standard practices and the extent to which research, rather than individual patient care, is involved.

Practitioners may be concerned that the off-label use of an approved drug may invite a variety of legal actions. To conform to accepted professional standards, the off-label use of a drug should be done in good faith, in the best interest of the patient, and without fraudulent intent. A practitioner may be accountable for the negligent use of any drug in a civil action, regardless of whether the FDA has approved the use of that drug. Labeling is not intended to preclude the practitioner from using his or her best medical judgment in the interest of patients or to impose liability for off-label use. Indeed, the practice of medicine will more than likely require a practitioner to use drugs off label to provide the most appropriate treatment of a patient. However, because the use of drugs in an off-label capacity can increase the liability risk for a practitioner should an adverse event or poor outcome ensue, it is essential that practitioners document the decision-making process to use a drug off label in the patient's medical record.

FEDERAL LEGISLATION TO INCREASE DRUG TESTING IN CHILDREN

The BPCA and the PREA are 2 complementary federal laws that have substantially increased clinical evaluation and labeling of drugs in children both by the pharmaceutical industry and through government-sponsored trials.[8] The PREA mandates that almost all new drugs and certain approved drugs must be studied in children for approved uses of the product if there is potential for use of that drug in children and that the application for new drug approval include the results of adequate pediatric studies unless the studies are deferred or waived by the FDA. The BPCA allows sponsors to qualify for an additional 6 months of market exclusivity if the sponsor completes and submits pediatric studies to the FDA, as outlined in an FDA-issued written request. A written request may include off-label as well as approved uses of a drug. In addition, the BPCA authorizes the National Institutes of Health, in conjunction with the FDA

and physicians from clinical disciplines, to work together to assign priority for testing of specific drugs in children. The National Institutes of Health, acting through the Eunice Kennedy Shriver National Institute of Child Health and Human Development, then solicits proposals for pediatric drug testing concordant with the drug prioritization recommendations and funds clinical studies that are judged meritorious by external review. The ratification of these 2 laws has been considered a significant success, because there have been more than 500 pediatric labeling changes. Also as a result of these laws, increased prospective pediatric drug testing has occurred via industry-sponsored studies, investigator-initiated studies, and consortia, such as the National Institute of Child Health and Human Development–funded Pediatric Trials Network. The net result has been an expansion of both pediatric labeling information and the knowledge base from which practitioners can draw to make informed therapeutic decisions.[12,13]

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act,[14] reauthorizing and strengthening the BPCA and PREA. The legislation aims to ensure that pediatric evaluations under PREA are conducted earlier in the drug development process to improve the quality of and accountability for completion of such studies and to advance the neonatal drug studies under the BPCA and PREA. The legislation also makes both the BPCA and PREA permanent law.

CONCLUSIONS

Off-label drug use remains an important public health issue, especially for infants, young children, and children with rare diseases. Evidence, not label indication, remains the gold standard from which practitioners should draw when making therapeutic decisions for their patients. The PREA and BPCA have been extremely successful and represent an essential first step in expanding this evidence as a means of achieving the ultimate goal that any and all drugs used to treat children will have age-appropriate evidence sufficient to provide information for labeling. However, labeling with pediatric information still exists in less than 50% of products,[15] such that much work remains to be done to ensure the best possible practice for therapeutic decision-making in pediatrics.

RECOMMENDATIONS

1. The practitioner who prescribes a drug is responsible for deciding which drug and dosing regimen the patient will receive and for what purpose.
   a. This decision should be made on the basis of the information contained in the drug's labeling (when available) or other data available to the prescriber.
   b. The use of a drug, whether off or on label, should be based on sound scientific evidence, expert medical judgment, or published literature whenever possible.
   c. Off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature.
2. Pediatricians should continue to advocate for necessary incentives and requirements to promote the study of drugs in children.
3. Physician researchers are encouraged to continue the rational and critical study of drugs in children through conducting and/or collaborating in well-designed pediatric drug studies, including national consortium studies.
4. Journals should be encouraged to publish the results of all well-designed investigations, including negative studies.
5. Institutions and payers should not use labeling status as the sole criterion that determines the availability on formulary or reimbursement status for medications in children. Similarly, less expensive therapeutic alternatives considered appropriate for adults should not automatically be considered appropriate first-line treatment in children. Finally, off-label uses of drugs should be considered when addressing various drug-related concerns, such as drug shortages.

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REFERENCES

1. American Academy of Pediatrics Committee on Drugs. Uses of drugs not described in the package insert (off-label uses). *Pediatrics*. 2002;110(1 pt 1):181–183
2. Best Pharmaceuticals for Children Act. Pub L No. 107-109 (2002)
3. Pediatric Research Equity Act. Pub L No. 108-155 (2003)
4. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med*. 2007;161(3):282–290
5. US Food and Drug Administration. Code of Federal Regulations Title 21. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3. Accessed November 20, 2012
6. US Food and Drug Administration. "Off-label" and investigational use of marketed drugs, biologics, and medical devices: information sheet. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm. Accessed January 19, 2014
7. Drug Amendments of 1962. Part A: amendments to assure safety, effectiveness, and reliability. Pub L No. 87-781, §101-308
8. Applications for FDA approval to market a new drug. Adequate and well-controlled studies. (2000) (codified at 21 CFR §314.126)
9. Public Health Service Act. 42 USC §262 (1999)
10. *Blazoski v Cook*, 346 NJ Super 256, 787 A2d 910 (2002)
11. *Shadrick v Coker*, 963 SW2d 726, 733 (Tenn 1998)
12. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290(7):905–911
13. Steinbrook R. Testing medications in children. *N Engl J Med*. 2002;347(18):1462–1470
14. Food and Drug Administration Safety and Innovation Act. Pub L No. 112-144 (2012)
15. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy MD. Pediatric information in drug product labeling. *JAMA*. 2012;307(18):1914–1915

Off-Label Use of Drugs in Children

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Original article

Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth

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Keywords: Transgender; Nonbinary; Gender-affirming care; Suicide; Depression; LGBTQ

A B S T R A C T

Purpose: There are no large-scale studies examining mental health among transgender and nonbinary youth who receive gender-affirming hormone therapy (GAHT). The purpose of this study is to examine associations among access to GAHT with depression, thoughts of suicide, and attempted suicide among a large sample of transgender and nonbinary youth.
Methods: Data were collected as part of a 2020 survey of 34,759 lesbian, gay, bisexual, transgender, queer, and questioning youth aged 13–24, including 11,914 transgender or nonbinary youth. Adjusted logistic regression assessed whether receipt of GAHT was associated with lower levels of depression, thoughts of suicide, and attempted suicide among those who wanted to receive GAHT.
Results: Half of transgender and nonbinary youth said they were not using GAHT but would like to, 36% were not interested in receiving GAHT, and 14% were receiving GAHT. Parent support for their child's gender identity had a strong relationship with receipt of GAHT, with nearly 80% of those who received GAHT reporting they had at least one parent who supported their gender identity. Use of GAHT was associated with lower odds of recent depression (adjusted odds ratio [aOR] = .73, $p < .001$) and seriously considering suicide (aOR = .74, $p < .001$) compared to those who wanted GAHT but did not receive it. For youth under age 18, GAHT was associated with lower odds of recent depression (aOR = .61, $p < .01$) and of a past-year suicide attempt (aOR = .62, $p < .05$).
Conclusions: Findings support a relationship between access to GAHT and lower rates of depression and suicidality among transgender and nonbinary youth.

IMPLICATIONS AND CONTRIBUTION

Transgender and nonbinary youth have high risk of depression and suicide. Gender-affirming healthcare is associated with lower risk using adult samples. This large-scale study examines GAHT among transgender and nonbinary youth. Findings demonstrate that GAHT is significantly related to lower rates of depression and suicidality among transgender and nonbinary youth.

Transgender and nonbinary youth are at elevated risk for depression, thoughts of suicide, and attempted suicide compared to youth who are cisgender and heterosexual, as well as cisgender members of the lesbian, gay, bisexual, transgender, queer, and questioning (LGBTQ) community [1–3]. Mental health disparities among transgender and nonbinary youth stem from minority stress based on the harmful ways transgender and nonbinary youth are treated by others [4]. Feelings of gender dysphoria associated with incongruence between one's physical traits and gender identity are also associated with mental health challenges for transgender and nonbinary youth [5]. As such, both the treatment of gender dysphoria and the reduction of minority stress offer pathways toward reducing disparities in depression and suicidality found among transgender and nonbinary youth.

Conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose.

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The Minority Stress Model details how chronic stressful events such as gender identity–based stigma and rejection produce proximal processes such as internalized stigma and shame, which result in mental health challenges [6]. Although minority stress is associated with greater risk of anxiety, depression, and suicidality among transgender and nonbinary individuals [2,5], gender-affirming medical care has been associated with lower risk [7,8]. Gender-affirming medical care is one component of the larger process of gender affirmation, which may include social, legal, and medical changes. Social transition is the primary and most common component of gender affirmation for prepubertal youth and involves allowing them to present in the way that feels most authentic to them. Medical-affirming care can include treatments that postpone physical changes associated with puberty, as well as treatments that lead to changes that would affirm one's gender identity. Gonadotropin-releasing hormone analogs, commonly known as "puberty blockers," are used to delay the onset of puberty, while gender-affirming hormone therapy (GAHT) is used to promote gender-affirming physical changes. GAHT allows transgender and nonbinary youth to develop physical characteristics that align with their gender identity and is appropriate for those who have begun puberty or following the use of puberty blockers. Access to GAHT is especially important during adolescence because some effects of puberty are not easily reversed by GAHT in adulthood (e.g., testosterone's effects on voice) [9]. Qualitative data highlight ways transgender individuals have experienced distress due to the delay in GAHT, which results in them undergoing puberty associated with their sex assigned at birth [10,11]. Access to GAHT is an ongoing issue for transgender youth and their families, both due to a lack of competent providers in many communities and due to recent legislative efforts to criminalize medical providers and parents who provide GAHT to youth under the age of 18 [12,13]. Barriers to care are often greater for transgender and nonbinary youth of color who are unrepresented in gender specialty clinics and have more difficulties accessing gender-affirming care compared to White transgender and nonbinary youth [9].

A recent study based on the 2015 U.S. Transgender Survey found that transgender adults who received pubertal blockers as adolescents had significantly lower lifetime suicidal ideation compared to those who desired but did not receive it [8]. However, thus far, there are no large-scale studies comparing mental health and suicidality among transgender and nonbinary youth who wanted GAHT and received it to those who wanted it but did not receive it [14]. Three small clinical studies have examined GAHT in relation to mental health and suicidality among transgender and nonbinary youth. However, these clinical studies were not able to randomize youth to receive GAHT or include a control group. The first study followed 47 transgender youth and found that mean levels of suicidality significantly decreased from 1.11 before starting GAHT to .27 when assessed approximately 1 year after beginning GAHT [7]. The second study of 128 transgender youth found small to moderate improvements in self-reported depressive symptoms (d = .44) [15]. The third study examined 50 transgender youth at two 6-month intervals following the start of GAHT and found significant decreases in depression as measured by the Center for Epidemiologic Studies Depression Scale [16]. Each of these studies noted limitations related to not being able to control for the role of parental support, as each youth had at least one parent who supported their receipt of GAHT.

The present study draws from a large sample of transgender and nonbinary youth between the ages of 13–24 to examine the association between receipt of GAHT with self-reported depression, thoughts of suicide, and attempted suicide. Furthermore, because many current concerns around GAHT relate to their use in youth under the age of 18, these associations will also be examined separately for those under age 18.

Methods

Procedure

Data were from an online nonprobability sample collected between October and December 2020 of 34,759 youth aged 13–24 who resided in the U.S. and identified as LGBTQ. Youth were recruited via targeted ads on Facebook, Instagram, and Snapchat. Those who reported residing outside of the U.S., having an age below 13 or above 24, or being both heterosexual and cisgender were excluded from the sample. To approach a more representative sample, targeted recruitment was conducted to ensure adequate sample sizes with respect to geography and race/ethnicity. Qualified respondents completed a secure online questionnaire that included a maximum of 142 questions. The survey employed two validity checks. The first was an item that required youth to select a specific response from the provided list. The second validity check screened for youth who responded inconsistently to the same item placed at two separate points in the survey. Each question related to mental health and suicidality was preceded by a message stating: "If at any time you need to talk to someone about your mental health or thoughts of suicide, please call The Trevor Project at 1-866-488-7386." Youth were able to select "decline to answer" for any questions in the survey that they did not want to answer. Respondents were eligible to be entered into a drawing for one of 100 gift cards worth $50 each by providing their email address after being routed to a separate survey. The research proposal was reviewed and approved by an independent Institutional Review Board, Solutions IRB. Youth participation was voluntary, and informed consent was obtained. We obtained a waiver of parental consent for youth aged 13–17 years as the research posed a minimal risk and could have presented potential harm for youth who were not out to their parents about their LGBTQ identity. No names or personal details were included to ensure confidentiality and privacy.

Measures

Gender-affirming hormone therapy use. Youth who indicated they were transgender or nonbinary were asked, "Are you currently taking gender-affirming hormones?" with response options that included, (1) "No, and I do not want to take them," (2) "No, but I would like to take them," and (3) "Yes." In logistic regression analyses, youth responses are coded as (0) "No, but I would like to take them" and (1) "Yes."

Depression. Current levels of depression were measured using the Patient Health Questionnaire-2 [17]. The Patient Health Questionnaire-2 was designed as a two-item screening tool for major depressive disorder in the past 2 weeks. Scores were dichotomized based on recommended guidelines for a total score of three or more being indicative of depression.

Suicidal thoughts and behaviors. Youth were first presented with a question on whether they had seriously considered suicide in the past year. Those that answered, "yes" were subsequently asked how many times they had attempted suicide in the past year, with answers dichotomized into zero compared to one or more attempts. Both items are from the Centers for Disease Control and Prevention's Youth Risk Behavior Survey [18].

Demographic covariates. The following sociodemographic covariates were examined based on their potential relationships with suicidality and access to GAHT: age, socioeconomic status (just able to meet basic needs or less, more than able to meet basic needs), race (Alaska Native/American Indian, Asian/Pacific Islander, Black/African American, Latinx, multiracial, or White), and census region (Northeast, South, Midwest, West). Gender identity was measured using a two-stage question that first asked, "What sex were youth assigned at birth, on your original birth certificate," with response options of male or female. The second question asked, "Which of the following terms best describes your gender identity. We understand that there are many different ways youth identify, please pick the one that best describes you," with response options of boy/man, girl/woman, and nonbinary/genderfluid/gender nonconforming, as well as options to indicate the youth did not understand the question or were not sure of their gender identity. For those who indicated a known gender identity, the measures were combined to create categories of transgender girl/woman, transgender boy/man, and nonbinary. A single item was used to measure sexual orientation stating, "Which of these options best describes your sexual orientation. We understand that there are many different sexual identities please pick the one that best describes you," with response options of gay, lesbian, bisexual, pansexual, queer, questioning, or straight/heterosexual [19].

Additional covariates. Four additional covariates were included based on their potential relationships with both access to GAHT and risk of depression and suicidality among transgender and nonbinary youth. Parent support for a youth's gender identity was assessed by asking youth, "Do you have at least one parent who is supportive of your gender identity?" with answers of (1) "No," (2) "Yes," and (3) "I am not 'out' about my gender to any of my parents." Youth's report of victimization based on their gender identity was assessed by asking, "Have you ever felt physically threatened or been physically abused because of your gender identity?" Response options were (0) "No" and (1) "Yes." Receipt of puberty blockers was assessed by an item placed immediately prior to the question on GAHT that asked, "Did you take medication designed to prevent or delay puberty (also known as puberty blockers)?" Response options were codes as (0) "No" and (1) "Yes." Exposure to gender identity conversion efforts (GICE) was assessed by asking, "Did you ever receive treatment from someone who tried to change your sexual orientation or gender identity (such as trying to make you straight or cisgender)?" Youth who did not undergo conversion efforts or who reported that they underwent conversion efforts related to only their sexual orientation were coded as (0) "No," while youth who reported undergoing GICE were coded as (1) "Yes."

Data analysis

SPSS version 28 was used in conducting all analyses [20]. Chi-squared tests of independence were used to examine the proportion of young people who used GAHT compared to those who wanted GAHT but did not receive it. A *t*-test was used to examine mean age differences. After adjustment for the aforementioned covariates, logistic regression was used to determine the odds of depression, past-year thoughts of suicide, and a past-year suicide attempt among those who received GAHT in comparison with those who wanted GAHT but did not receive it. To address the lack of research focused on gender-affirming medical care among transgender and nonbinary youth who are minors, analyses were also conducted separately among youth aged 13–17.

Participants

A total of 11,914 youth from unique IP address indicated that they were transgender or nonbinary. Our question on GAHT was placed toward the end of the survey, and as such 2,895 youth had missing data. Chi-squared tests of independence were used to compare the 9,019 youth who had GAHT data to the 2,895 who did not. There were no significant differences within sexual identity, socioeconomic status, census region, gender identity support from parents, gender identity-based victimization, or GICE. The proportion of transgender boys/men and nonbinary youth were comparable. There were slightly higher rates of transgender women in the sample with data on GAHT compared to those with missing data (8% vs. 6%, $\chi^2(2) = 13.21$, $p = .001$). The sample with data on GAHT had higher rates of multiracial youth (21% vs. 17%) and lower rates of White youth (55% vs. 60%) ($\chi^2(5) = 34.32$, $p < .001$). Age was examined using *t*-test analyses with the average age of the subset of youth with data on GAHT slightly greater (17.62) than those without it (17.30), $t(11{,}912 = 4.60)$, $p < .001$.

Results

The majority of youth were nonbinary (63%), followed by transgender boy/man (29%) and transgender girl/woman (8%). The average age was 17.62 (standard deviation = 3.21), and 27% reported that they were either just able to financially meet basic needs or struggled to meet basic needs. Most youth resided in the South (36%), followed by West (27%), Midwest (22%), and Northeast (15%). Overall, 29% identified as bisexual, 26% as pansexual, 20% as gay or lesbian, 20% as queer, 4% as questioning, and 2% as heterosexual. The majority of the sample was non-Hispanic White (55%), followed by multiracial (21%), Latinx (12%), Asian/Pacific Islander (5%), Black (4%), and American Indian/Alaskan Native (2%).

Half of transgender and nonbinary respondents said they were not using GAHT but would like to receive it, 36% said they were not interested in receiving GAHT, and 14% said they were receiving GAHT. In bivariate analyses (Table 1), those who received GAHT were on average older, and a greater proportion reported that they struggled to meet basic needs or were just able to meet them, compared to those who wanted GAHT but did not receive it. Those who lived in the South were underrepresented among those who received GAHT when they desired it. Transgender girls/women and transgender boys/men were represented in greater proportions among those who received GAHT, while a greater proportion of those who were nonbinary reported wanting GAHT but not receiving it. White youth were the only race/ethnicity group that were represented in a greater proportion among those who received GAHT compared to those who wanted it but did not receive it. Transgender and nonbinary

Table 1
Sample characteristics of transgender and nonbinary youth aged 13–24 based on receipt of GAHT

	Received GAHT (n = 1,216) Mean (SD) or % (n)	Wanted but did not receive GAHT (n = 4,537) Mean (SD) or % (n)	
Age	19.95 (2.80)	16.91 (2.97)	$t(15{,}751) = 33.26$, $p < .001$
Socioeconomic status			$\chi^2(1) = 17.11$, $p < .001$
More than meets basic needs	67.3 (794)	73.5 (2,947)	
Just meets basic needs or less	32.7 (385)	26.5 (1,063)	
Census region			$\chi^2(3) = 32.25$, $p < .001$
Northeast	17.2 (209)	14.0 (634)	
South	28.7 (349)	36.9 (1,676)	
Midwest	23.4 (285)	22.8 (1,035)	
West	30.7 (373)	26.3 (1,192)	
Gender identity			$\chi^2(2) = 374.88$, $p < .001$
Nonbinary	21.3 (259)	49.5 (2,245)	
Transgender boy/man	55.3 (673)	41.3 (1,874)	
Transgender girl/woman	23.4 (284)	9.2 (418)	
Sexual identity			$\chi^2(5) = 113.49$, $p < .001$
Gay/lesbian	25.6 (310)	17.9 (807)	
Heterosexual	4.5 (53)	1.8 (80)	
Bisexual	30.5 (369)	29.4 (1,325)	
Pansexual	16.4 (198)	27.8 (1,250)	
Queer	20.2 (244)	19.0 (845)	
Questioning	2.9 (35)	4.4 (196)	
Race/ethnicity			$\chi^2(5) = 63.34$, $p < .001$
American Indian/Alaskan Native	1.4 (16)	2.2 (98)	
Asian/Pacific Islander	3.1 (36)	4.6 (202)	
Black	1.7 (20)	3.4 (150)	
Latinx	8.8 (104)	12.4 (543)	
White	68.3 (805)	55.8 (2,441)	
Multiracial	16.7 (197)	21.5 (940)	

GAHT = gender-affirming hormone therapy; SD = standard deviation.

youth who identified as gay, lesbian, or heterosexual were represented in higher proportions among those who received GAHT compared to those who wanted it but did not receive it. Pansexual youth were underrepresented among those who wanted GAHT but did not receive it. Table 2 presents the characteristics of transgender and nonbinary youth among the

Table 2
Sample characteristics of transgender and nonbinary youth aged 13–17 based on receipt of GAHT

	Received GAHT (n = 274) Mean (SD) or % (n)	Wanted but did not receive GAHT (n = 2,961) Mean (SD) or % (n)	
Age	16.00 (1.03)	15.09 (1.36)	$t(13{,}233) = 10.81$, $p < .001$
Socioeconomic status			$\chi^2(1) = 3.77$, $p = .05$
More than meets basic needs	86.3 (220)	81.3 (2,019)	
Just meets basic needs or less	13.7 (35)	18.7 (463)	
Census region			$\chi^2(3) = 14.50$, $p < .01$
Northeast	14.6 (40)	13.7 (405)	
South	26.3 (72)	37.4 (1,107)	
Midwest	24.8 (68)	22.0 (652)	
West	34.3 (94)	26.9 (797)	
Gender identity			$\chi^2(2) = 100.35$, $p < .001$
Nonbinary	15.3 (42)	46.7 (1,382)	
Transgender boy/man	74.8 (205)	46.5 (1,377)	
Transgender girl/woman	9.9 (27)	6.8 (202)	
Sexual identity			$\chi^2(5) = 52.85$, $p < .001$
Gay/lesbian	32.2 (88)	18.5 (544)	
Heterosexual	4.0 (11)	1.6 (46)	
Bisexual	33.0 (90)	31.3 (921)	
Pansexual	13.9 (38)	16.5 (486)	
Queer	13.6 (37)	27.0 (795)	
Questioning	3.3 (9)	5.0 (148)	
Race/ethnicity			$\chi^2(5) = 14.31$, $p = .01$
American Indian/Alaskan Native	1.9 (5)	2.5 (71)	
Asian/Pacific Islander	4.2 (11)	5.4 (152)	
Black	1.5 (4)	3.9 (111)	
Latinx	8.1 (21)	14.0 (396)	
White	58.8 (153)	50.2 (1,424)	
Multiracial	25.4 (66)	24.1 (683)	

GAHT-gender-affirming hormone therapy; SD = standard deviation.

Table 3
Challenges among transgender and nonbinary youth aged 13–24 based on receipt of GAHT

	Received GAHT (n = 1,216) % (n)	Wanted but did not receive GAHT (n = 4,537) % (n)	
Gender support from parents			$\chi^2(2) = 695.98, p < .001$
No	17.6 (210)	33.6 (1,451)	
Yes	79.8 (955)	38.2 (1,648)	
Not "out" to parents	2.6 (31)	28.2 (1,218)	
Gender identity-based victimization	61.9 (734)	49.2 (2,125)	$\chi^2(1) = 59.56, p < .001$
Gender identity conversion efforts	14.7 (172)	13.9 (581)	$\chi^2(1) = 0.42, p = .52$
History of puberty blocker use	11.0 (132)	1.0 (44)	$\chi^2(1) = 315.80, p < .001$
Depression	60.8 (738)	75.0 (3,385)	$\chi^2(1) = 95.38, p < .001$
Seriously considered suicide	43.9 (521)	57.1 (2,409)	$\chi^2(1) = 65.89, p < .001$
Attempted suicide	14.6 (173)	23.2 (956)	$\chi^2(1) = 40.24, p < .001$

GAHT = gender-affirming hormone therapy.

subsample aged 13–17 based on whether they were able to obtain desired GAHT.

Those who had parental support for their gender identity comprised nearly 80% of youth who received GAHT. Among those who wanted GAHT but did not receive it, 38% had parental support (Table 3). Among those who received GAHT, 11% reported that they had ever used puberty blockers compared to only 1% of those who wanted GAHT but did not receive it. Less than 1% (.6%) of youth who reported not wanting GAHT had ever used puberty blockers. A higher percentage of youth who received GAHT experienced gender identity–based victimization compared to those who wanted GAHT but did not receive it. In bivariate analysis, a smaller percentage of transgender and nonbinary youth who received GAHT reported recent depression (61% vs. 75%), seriously considering suicide in the past year (44% vs. 57%) and attempting suicide in the past year (15% vs. 23%) compared to those who wanted GAHT but did not receive it. Similar patterns emerged among youth aged 13–17 compared to the full sample (Table 4); however, 94% of those 13–17 who received GAHT had parental support compared to 80% among the full sample. Additionally, a larger proportion of those aged 13–17 who received GAHT had used puberty blockers (24%) compared to the overall sample (11%).

In adjusted logistic regression models (Table 5), receipt of GAHT was associated with lower odds of recent depression (adjusted odds ratio [aOR] = .73, $p < .001$) and seriously considering suicide in the past year (aOR = .74, $p < .001$). The aOR for attempted suicide among the overall sample of transgender and nonbinary youth aged 13–24 did not reach statistical significance (aOR = .84, $p = .16$). Among those aged 13–17, receipt of GAHT was associated with nearly 40% lower odds of recent depression (aOR = .61, $p < .01$) and attempting suicide in the past year (aOR = .62, $p < .05$). For youth under age 18, the aOR for seriously considering suicide in the past year did not reach statistical significance (aOR = .74, $p = .08$).

Discussion

These findings extend previous cross-sectional research conducted with transgender and nonbinary adults and provide support for a significant relationship between access to GAHT and lower depression and suicidality among transgender and nonbinary youth. Among the full sample and those under age 18, receipt of GAHT was associated with significantly lower odds of experiencing symptoms of depression in the previous 2 weeks. Although our study is not able to determine temporal patterns, it is unlikely that many transgender and nonbinary youth began GAHT subsequent to this 2-week time frame. The pattern of statistical significance for findings related to past-year suicidality was less consistent, which may indicate challenges related to statistical power when examining fairly infrequent outcomes such as suicidal thoughts and behaviors, particularly among smaller subgroups of individuals [21]. However, overall, our results indicate significant relationships between receipt of GAHT and lower suicidality among transgender and nonbinary youth.

Bivariate findings point to disparities in receipt of GAHT among subgroups of transgender and nonbinary youth. In particular, transgender and nonbinary youth living in the South had lower rates of accessing GAHT when they wanted it. This is also the region where the majority of bills to restrict access to gender-affirming care for transgender youth have been introduced subsequent to the collection of these data [22]. Overall youth who were able to

Table 4
Challenges among transgender and nonbinary youth aged 13–17 based on receipt of GAHT

	Received GAHT (n = 274) % (n)	Wanted but did not receive GAHT (n = 2,961) % (n)	
Gender support from parents			$\chi^2(2) = 323.26, p < .001$
No	3.7 (10)	33.3 (933)	
Yes	93.7 (254)	37.2 (1,043)	
Not "out" to parents	2.6 (7)	29.5 (825)	
Gender identity-based victimization	57.5 (734)	48.6 (2,125)	$\chi^2(1) = 7.66, p < .01$
Gender identity conversion efforts	13.1 (34)	13.6 (364)	$\chi^2(1) = 0.05, p = .82$
History of puberty blocker use	24.4 (66)	1.3 (37)	$\chi^2(1) = 422.86, p < .001$
Depression	60.9 (167)	77.9 (2,294)	$\chi^2(1) = 39.83, p < .001$
Seriously considered suicide	51.1 (135)	61.6 (1,674)	$\chi^2(1) = 10.97, p < .001$
Attempted suicide	16.0 (42)	27.7 (733)	$\chi^2(1) = 16.67, p < .001$

GAHT = gender-affirming hormone therapy.

Table 5
Multivariate adjusted logistic regression of gender-affirming hormone therapy on depression and suicidality among transgender and nonbinary youth

	Overall sample		Ages 13–17	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Depression	0.73 (0.61–0.88)	<.001	0.61 (0.43–0.86)	<.01
Seriously considered suicide	0.74 (0.62–0.88)	<.001	0.74 (0.52–1.03)	.08
Attempted suicide	0.84 (0.66–1.07)	.16	0.62 (0.40–0.97)	.04

Adjusted for age, socioeconomic status, census region, gender identity, sexual orientation, race/ethnicity, parent support for gender identity, gender identity-based victimization, gender identity conversion efforts, and history of puberty blocker use.
aOR = adjusted odds ratio; CI = confidence interval.

access GAHT reported greater rates of financial struggles; however, this was not true for the subsample aged 13–17. Our measure of socioeconomic status was based on household finances, which often look different for those 18 and older who may no longer be able to rely on their family's resources. As expected, youth over age 18 had higher rates of being able to access GAHT when they desired it. Among transgender and nonbinary youth, those who primarily reported a binary identity (i.e., transgender man or transgender woman) had higher rates of accessing GAHT compared to those who were nonbinary. Pansexual youth were also underrepresented among those who received GAHT; however, this relationship may also be related to nonbinary identities as pansexual was the most frequently reported sexual orientation among nonbinary youth. There were also disparities in access to GAHT across race/ethnicity. White youth represented 68% of those who received GAHT compared to 56% among those who wanted it but did not receive it, with LGBTQ youth of color reporting lower rates of obtaining GAHT. Furthermore, parental support for their child's gender identity had a strong relationship with receipt of GAHT, with nearly 80% of those who received GAHT reporting they had at least one parent who supported their gender identity, including 94% of those aged 13–17. Together, these findings indicate that youth receipt of gender-affirming care is based not only on their presenting concerns but also on their parent's level of support, geography, and their social identities, which relate to barriers to care among the broader population of youth as well [23–26]. To reduce disparities in youth access to GAHT there is a need to focus on increasing awareness and education around gender-affirming care for parents as well as among healthcare providers and others in positions to support youth health and well-being.

Some of the hesitance regarding gender-affirming care for transgender and nonbinary youth may be due to a misunderstanding of the causes of mental health challenges in transgender and nonbinary individuals, such as a failure to recognize ways incongruence between physical traits and one's gender identity can produce psychological distress marked by depression. High rates of depression, suicidal ideation, and suicide attempts among transgender youth are sometimes used by antitransgender politicians and activists to erroneously suggest that transgender identity is a mental health condition that can be treated through counseling and conversion efforts [27]. These individuals ignore the impacts of gender dysphoria and minority stress [28] and suggest that GAHT is not necessary if transgender youth can be counseled into accepting their sex assigned at birth. The findings of this study demonstrate that GAHT could be a potential mechanism by which mental health and suicide disparities among transgender and nonbinary youth may begin to decrease. Furthermore, existing evidence suggests that regret is low for gender-affirming care interventions, with one study of 55 transgender adults who had received gender-affirming care as adolescents finding that not one experienced regret [29].

There remains a critical need for mental health outcomes data among transgender and nonbinary youth receiving GAHT, including through longitudinal studies. Large-scale longitudinal data collection will better elucidate the risks and benefits of individual treatment options so that youth and their families can make evidence-informed decisions regarding care.

Limitations

This study boasts a large, diverse sample of transgender and nonbinary youth across the U.S.; however, some limitations should also be noted. First, causation cannot be inferred due to the study's cross-sectional design. It is possible that those who historically have higher rates of depression and suicidal thoughts and behaviors are also less able to seek or obtain GAHT. However, combined with repeated measures designs of other studies [7,15] it appears likely that receipt of GAHT may lead to reduced levels of depression and suicidality. Given existing research, it is unlikely that randomized controlled trials of GAHT for youth would be ethically appropriate. To better understand directionality, prospective longitudinal designs are needed. Additionally, our self-reported non-probability sample may limit the generalizability of findings and suggest the need for the inclusion of gender identity-specific measures in larger probability samples. Finally, our study did not include variables to assess at what age youth began puberty blockers or GAHT or the duration for which they had been receiving them. Because younger transgender and nonbinary youth in our sample may have been eligible for either puberty blockers or GAHT, there may have been youth who were currently receiving the puberty blockers and not yet ready to start GAHT. However, this is a small part of our sample as only 20 youth aged 13–14 indicated that they had taken puberty blockers but had not accessed desired GAHT. Data on age and duration of access should be included in future studies to better understand the relationship between GAHT and mental health.

Unfortunately, efforts to legally restrict gender-affirming care for transgender and nonbinary youth may negatively impact mental health through two separate but linked pathways. The first is by directly prohibiting medication that many of these youth rely on to reduce feelings of gender dysphoria. The second is by increasing minority stress through negative public attention and harmful rhetoric debating the rights of transgender and nonbinary youth to live their lives authentically. As such, efforts to address the mental health of transgender and nonbinary youth must also acknowledge and address the cumulative risk that antitransgender political statements and legislative efforts may have on their well-being.

As the evidence for gender-affirming care grows, medical and mental health organizations are increasingly expressing support for it. Many major medical and mental health organizations have guidelines for working with transgender individuals centered around respect for the patient and shared decision-making [30,31], with some organizations releasing statements explicitly opposing any efforts to prevent access to gender-affirming care [32,33]. Given the well-documented risks of negative mental health and suicide among transgender and nonbinary youth, it is necessary that those serving these youth provide care that is patient-centered, affirming, and evidence-based.

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References

[1] Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students — 19 states and large urban school districts, 2017. MMWR Morb Mortal Wkly Rep 2019;68:67–71.
[2] Price-Feeney M, Green AE, Dorison S. Understanding the mental health of transgender and nonbinary youth. J Adolesc Health 2020;66:684–90.
[3] Toomey RB, Syvertsen AK, Shramko M. Transgender adolescent suicide behavior. Pediatrics 2018;142:e20174218.
[4] Meyer IH. Resilience in the study of minority stress and health of sexual and gender minorities. Psychol Sex Orientat Gend Divers 2015;2:209–13.
[5] Chodzen G, Hidalgo MA, Chen D, Garofalo R. Minority stress factors associated with depression and anxiety among transgender and gender-nonconforming youth. J Adolesc Health 2019;64:467–71.
[6] Hendricks M, Testa R. A conceptual framework for clinical work with transgender and gender nonconforming clients: An adaptation of the minority stress model. Prof Psychol Res Pract 2012;43:460–7.
[7] Allen L, Watson L, Egan A, Moser C. Well-being and suicidality among transgender youth after gender-affirming hormones. Clin Pract Pediatr Psychol 2019;7:302–11.
[8] Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics 2020;145:e20191725.
[9] Call DC, Challa M, Telingator CJ. Providing affirmative care to transgender and gender diverse youth: Disparities, interventions, and outcomes. Curr Psychiatry Rep 2021;23:1–10.
[10] Raj S. Alleviating anxiety and cultivating care: Young trans people in the family court of Australia. Aust Fem L J 2019;45:111–30.
[11] Riggs DW, Bartholomaeus C, Sansfacon AP. 'If they didn't support me, I most likely wouldn't be here': Transgender young people and their parents negotiating medical treatment in Australia. Int J Transgend Health 2020;21:3–15.
[12] Gridley SJ, Crouch JM, Evans Y, et al. Youth and caregiver perspectives on barriers to gender-affirming health care for transgender youth. J Adolesc Health 2016;59:254–61.
[13] Kremen J, Williams C, Barrera EP, et al. Addressing legislation that restricts access to care for transgender youth. Pediatrics 2021;147:e2021049940.
[14] Chew D, Anderson J, Williams K, et al. Hormonal treatment in young people with gender dysphoria: A systematic review. Pediatrics 2018;141:e20173742.
[15] Kuper LE, Stewart S, Preston S, et al. Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. Pediatrics 2020;145:e20193006.
[16] Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. Int J Pediatr Endocrinol 2020;2020:1–5.
[17] Richardson LP, Rockhill C, Russo JE, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. Pediatrics 2010;125:e1097–103.
[18] Johns MM, Lowry RR, Haderxhanaj LT, et al. Trends in violence victimization and suicide risk by sexual identity among high school students — youth risk behavior survey, United States, 2015–2019. MMWR Morb Mortal Wkly Rep 2020;79:19–27.
[19] DeChants J, Green AE, Price MN, Davis C. Measuring youth sexual orientation and gender identity. The Trevor Project. 2021. Available at: https://www.thetrevorproject.org/2021/07/28/measuring-youth-sexual-orientation-and-gender-identity/. Accessed August 20, 2021.
[20] IBM Corp. IBM SPSS Statistics for Macintosh, version 26.0. Armonk, NY: IBM Corp; 2019.
[21] O'Connor RC, Portzky G. Looking to the future: A synthesis of new developments and challenges in suicide research and prevention. Front Psychol 2018;9:2139.
[22] Conron KJ, O'Neill K, Vasquez LA. Prohibiting gender-affirming medical care for youth. The Williams Institute UCLA School of Law. 2021. Available at: https://williamsinstitute.law.ucla.edu/publications/bans-trans-youth-health-care/. Accessed August 20, 2021.
[23] Alegría M, Alvarez K, Ishikawa RZ, et al. Removing obstacles to eliminating racial and ethnic disparities in behavioral health care. Health Aff (Millwood) 2016;35:991–9.
[24] Clark BA, Marshall SK, Saewyc EM. Hormone therapy decision-making processes: Transgender youth and parents. J Adolesc 2020;79:136–47.
[25] Schnyder N, Lawrence D, Panczak R, et al. Perceived need and barriers to adolescent mental health care: Agreement between adolescents and their parents. Epidemiol Psychiatr Sci 2019;29:1–9.
[26] Hodgkinson S, Godoy L, Beers LS, Lewin A. Improving mental health access for low-income children and families in the primary care setting. Pediatrics 2017;139:e20151175.
[27] American Psychological Association. APA Resolution on gender identity change efforts. 2021. Available at: https://www.apa.org/about/policy/resolution-gender-identity-change-efforts.pdf. Accessed June 9 2021.
[28] Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental health of transgender children who are supported in their identities. Pediatrics 2016;137:e20153223.
[29] De Vries AL, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696–704.
[30] American Psychiatric Association. Position statement on access to care for transgender and gender diverse individuals. 2018. Available at: https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-2018-Discrimination-Against-Transgender-and-Gender-Diverse-Individuals.pdf. Accessed May 14, 2021.
[31] Rafferty J, Committee on Psychosocial Aspects of Child and Family Health. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. Pediatrics 2018;142:e20182162.
[32] Beers LS. American Academy of Pediatrics Speaks out against bills harming transgender youth. 2021. Available at: https://services.aap.org/en/news-room/news-releases/aap/2021/american-academy-of-pediatrics-speaks-out-against-bills-harming-transgender-youth/. Accessed May 14, 2021.
[33] American Academy of Child & Adolescent Psychiatry. Policy statement on conversion therapy. 2018. Available at: https://www.aacap.org/AACAP/Policy_Statements/2018/Conversion_Therapy.aspx. Accessed August 26, 2019.

SEXUAL MEDICINE REVIEWS REVIEW

Feminizing Genital Gender-Confirmation Surgery

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ABSTRACT

Introduction: For many patients with gender dysphoria, gender-confirmation surgery (GCS) helps align their physical characteristics with their gender identity and is a fundamental element of comprehensive treatment. This article is the 2nd in a 3-part series about the treatment of gender dysphoria. Non-operative management was covered in part 1. This section begins broadly by reviewing surgical eligibility criteria, benefits of GCS, and factors associated with regret for transgender men and women. Then, the scope narrows to focus on aspects of feminizing genital GCS, including a discussion of vaginoplasty techniques, complications, and sexual function outcomes. Part 3 features operative considerations for masculinizing genital GCS.

Aim: To summarize the World Professional Association for Transgender Health's (WPATH) surgical eligibility criteria and describe how patients with gender dysphoria benefit from GCS, provide an overview of genital and non-genital feminizing gender-confirmation procedures, and review vaginoplasty techniques, preoperative considerations, complications, and outcomes.

Methods: A review of relevant literature through April 2017 was performed using PubMed.

Main Outcome Measures: Review of literature related to surgical eligibility criteria for GCS, benefits of GCS, and surgical considerations for feminizing genitoplasty.

Results: Most transgender men and women who satisfy WPATH eligibility criteria experience improved quality of life, overall happiness, and sexual function after GCS; regret is rare. Penile inversion vaginoplasty is the preferred technique for feminizing genital GCS according to most surgeons, including the authors whose surgical technique is described. Intestinal vaginoplasty is reserved for certain scenarios. After vaginoplasty most patients report overall high satisfaction with their sexual function even when complications occur, because most are minor and easily treatable.

Conclusion: GCS alleviates gender dysphoria for appropriately selected transgender men and women. Preoperative, intraoperative, and postoperative considerations of feminizing genital gender-confirmation procedures were reviewed. **Hadj-Moussa M, Ohl DA, Kuzon WM. Feminizing Genital Gender-Confirmation Surgery. Sex Med Rev 2018;6:457–468.**

Key Words: Gender Dysphoria; Transgender; Gender-Confirmation Surgery; Gender Reassignment; Vaginoplasty

INTRODUCTION

Gender-confirmation surgery (GCS) is an effective and medically necessary treatment for many patients with gender dysphoria.[1] GCS enhances the benefits of psychotherapy, social transition, and hormone therapy to alleviate gender dysphoria by maximizing physical characteristics congruent with a patient's gender identity. Contemporary studies support that appropriately selected patients who undergo GCS experience relief from gender dysphoria and improved emotional well-being and quality of life (QOL).[1–3] Patients also benefit from a wide range of procedures to alter their secondary sex characteristics (Table 1).

This article is the 2nd in a 3-part series focused on the comprehensive treatment of gender dysphoria. In part 1, the diagnosis and non-operative management of gender dysphoria, including psychotherapy, social gender transition, and hormone therapy, were reviewed.[4] In part 2, surgical eligibility criteria, factors associated with regret, and benefits of GCS for transgender men and women are reviewed before focusing on feminizing gender-confirmation procedures, including an overview of genital and non-ge aginoplasty

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Table 1. Gender-confirmation surgery

	Masculinizing surgery	Feminizing surgery
Face	Lipofilling	Facial feminization
	Liposuction	Thyroid chondroplasty
	Facial masculinization (rare)	Hair reconstruction
	Voice modification surgery (rare)	Voice modification surgery
Body	Subcutaneous mastectomy	Augmentation mammoplasty
	Male chest contouring	Lipofilling
	Pectoral implants	Gluteal augmentation
		Waist lipoplasty
Genital	Hysterectomy	Orchiectomy
	Salpingo-oophorectomy	Penectomy
	Vaginectomy	Vaginoplasty + clitoro-labioplasty
	Metoidioplasty ± urethral lengthening	Vulvoplasty + clitoro-labioplasty
	Phalloplasty ± urethral lengthening	
	Scrotoplasty	
	Testicular prosthesis placement	
	Penile prosthesis placement	

techniques, postoperative outcomes and complications, and the authors' operative technique for penile inversion vaginoplasty (PIV). Part 3 will focus on masculinizing GCS and review ancillary procedures and services that round out multidisciplinary treatment of gender dysphoria.

GENDER-CONFIRMATION SURGERY ELIGIBILITY CRITERIA

Health care professionals treating gender dysphoric patients are well advised to follow the Standard of Care (SOC) recommendations published by the World Professional Association for Transgender Health (WPATH), the pre-eminent professional organization dedicated to promoting high-quality evidence-based care for transgender patients.[1] The SOC establishes a framework for communication and interaction between the multidisciplinary and often geographically dispersed health care professionals caring for individual transgender patients. The WPATH's guidelines have been criticized for being rigid and paternalistic but that is not their intent. Rather than being interpreted as fixed "rules," the SOC explicitly states that interventions should be individualized for each patient and that deviation from the WPATH's recommendations is appropriate at times.[1] In addition, the SOC is under constant review and revised as knowledge and experience with this patient population grows; the 8th version of the SOC is currently being updated and has not been released.

A critical factor for high-quality transgender patient care is assessment by a mental health professional (MHP) who is knowledgeable about the assessment and treatment of gender dysphoria.[1] When a qualified MHP confirms a patient's readiness for GCS, the MHP can provide a referral to the appropriate surgeon. The WPATH SOC specifies that referrals for GCS from qualified MHPs should report the following[1]:

- Patient's gender dysphoria is persistent and well documented
- Patient has the capacity to make a fully informed decision and consent for treatment
- Patient is the legal age of majority in a given country
- Patient's medical or mental health comorbidities, including any psychiatric disorders, are "reasonably well controlled" (for chest surgery) or "well controlled" for genital surgery.[1] Obviously surgery should not be performed on actively psychotic patients.

The WPATH encourages individualized treatment based on each patient's specific goals for gender expression and thus does not specify which procedures should be done, or in what order.[1] Patients and their surgeons should come to a mutual agreement about which surgeries to perform, taking into account the patient's goals for GCS, realistic expectations regarding postoperative esthetic and functional outcomes, risk of morbidity, recovery times, and cost.

Non-Genital Surgery

The WPATH SOC does not require any letters of referral for facial feminization or masculinization procedures or for thyroid laryngoplasty. These procedures can be performed before, after, or independent of breast or chest or genital GCS.[1] To satisfy WPATH eligibility criteria for breast or chest GCS, patients should obtain 1 letter of referral from a qualified MHP.[1] Cross-sex hormone therapy is not a prerequisite for breast or chest surgery, although the WPATH encourages transgender women to be treated with at least 12 months of feminizing hormones before breast surgery because estrogen will stimulate breast development. In the authors' experience, many patients are satisfied with the breast size they achieve with estrogen therapy alone. Natural breast tissue also optimizes and stabilizes the postoperative cosmetic result for patients who opt to undergo breast augmentation surgery.[1]

Genital Surgery

WPATH eligibility criteria for genital GCS require 2 letters of referral from separate qualified MHPs and compliance, in the absence of a medical contraindication, with at least 12 months of continuous cross-sex hormone therapy.[1] Any patient undergoing metoidioplasty, phalloplasty, or vaginoplasty also must have completed a 12-month real-life social transition, living full time as their desired gender, to ensure they have resolved any personal, professional, or social issues surrounding their gender identity before undergoing irreversible genital surgery.[1] It should be noted that the 12-month real-life experience is the most heavily criticized stipulation of the SOC, viewed by some as a barrier to GCS. Psychotherapy is recommended but not required for patients undergoing genital GCS.

ROLE OF SURGEONS

GCS does not fall within a single specialty's scope of practice. Depending on the procedure and the surgeon's training and level of expertise, GCS is performed by plastic surgeons, urologists, general surgeons, otolaryngologists, and gynecologists. There is ongoing international discussion regarding the requisite training to perform GCS, especially genital procedures. Currently, there are very few residency training programs or fellowships that encompass GCS. In the absence of dedicated training curricula, board-certified surgeons intending to perform genital reconstruction should proceed with specialized training from experienced mentors.

Surgeons should confirm WPATH eligibility criteria have been met for each patient. This is ideally accomplished by maintaining a working relationship with other members of the patient's treatment team. GCS should be tailored to meet each patient's goals for gender expression so the WPATH recommends surgeons thoroughly discuss the options for each type of surgery with prospective patients including the benefits and drawbacks; realistic expectations for cosmetic and functional outcomes; financial obligations; and the risk of complications including how unsatisfactory outcomes are treated.[1] This information should be presented in advance of surgery, using layman's terms, and with the help of visual aids such as before and after photographs. Patients should be given a minimum of 24 hours to consider their options and have their questions answered before making the decision to proceed with surgery.[1] Informed consent must be documented for each procedure.

BENEFITS OF GENDER-CONFIRMATION SURGERY

Across all transgender health care research there is a paucity of high level-of-evidence studies. Reported case series are often from a single institution, samples are small, and reported outcome measures are inconsistent. Despite these limitations, the current body of published literature strongly suggests that most transgender patients who undergo GCS experience improved QOL, overall happiness, psychologic function, body image, and sexual satisfaction.[1,2,5–7]

A few higher-quality studies using validated QOL and patient-reported outcome measures are starting to be published. In 1 study 232 patients rated their QOL after GCS using a 21-point Likert scale ranging from −10 ("most worsening possible") to 10 ("most improvement possible) for an average score of 7.9 ± 2.6 (range = −2 to 10). The same cohort of patients rated their overall happiness with GCS with an average score of 8.7 ± 1.6 (range = 0−10).[8] In another study with a mean follow-up of almost 14 years, 68 patients rated their psychologic well-being after GCS from 1 ("worse than ever") to 5 ("better than ever") for an average score of 4.35 ± 0.86.[9] 96% of patients in a German study remarked that they would undergo GCS again.[10] Satisfaction with GCS remains high even when surgical complications occur, which likely reflects the importance of GCS for patients who above all are seeking relief from gender dysphoria.[8,9]

A small number of prospective studies measuring the impact of GCS also provide encouraging results. In a Brazilian study, 47 transgender men were evaluated before and 1 year after GCS using the World Health Organization Quality of Life Assessment (WHOQOL-100). Patients were found to have statistically significant improvements in psychologic (eg, positive feelings, self-esteem, body image) and social (eg, relationships, social support, sexual activity) domains. The same cohort did report worse physical health (pain and discomfort, energy and fatigue, sleep) and level of independence (mobility, activity of daily living), although the investigators suggested this finding could be related to the postoperative recovery period.[7] A prospective study of young transgender adults who underwent puberty suppression followed by cross-sex hormone therapy and GCS once they reached the age of consent showed that treatment was associated with statistically significant improvements in body image, psychological functioning, overall well-being, and decrease of gender dysphoria.[6]

Transgender patients describe their sexual function and sexual satisfaction, outcome measures associated with increased overall happiness and QOL, favorably after GCS.[2,5,8] After inversion vaginoplasty, transgender women in 1 study rated their sexual satisfaction with an average score of 7.8 ± 2.4 (range = 0−10).[8] In a retrospective study, trans-feminine and trans-masculine patients rated their postoperative sex lives on a scale from 1 ("very dissatisfied") to 5 ("very satisfied") for an average score of 3.42 ± 1.12 and 3.78 ± 1.07, respectively.[9] In a separate cohort of transgender men and women, 75.5% described an improved sex life after GCS, with some citing that they finally felt comfortable with their genitals.[5] Unfortunately, good postoperative sexual function is not ubiquitous; in the same study 12.3% of patients described worse sex lives after GCS because of genital pain, lack of sensation, and difficulty relaxing.[5]

REGRET AFTER GENDER-CONFIRMATION SURGERY

Regret after GCS is rare, occurring in 0% to 3.8% of patients.[9,11–13] Ongoing discrimination despite undergoing GCS can cause some patients to have difficulty expressing their

gender identity and regret having had surgery. Factors associated with regret include poor social and family support, late-onset gender transition, suboptimal cosmetic outcome, poor sexual function, concomitant mental health issues, and non-compliance with WPATH SOC guidelines.[11–14] In a study of patients requesting genital reversal surgery, Djordjevic et al[14] found that every patient had undergone GCS before meeting WPATH eligibility criteria by an insufficient social gender transition, absent or inappropriate hormone therapy, or evaluation by an improperly qualified MHP. Patterns that emerge from studies of regretful patients underscore the importance of adhering to WPATH SOC guidelines, which include rigorous training standards for MHPs who diagnose, treat, and refer gender dysphoric patients for GCS.[1]

FEMINIZING GENDER-CONFIRMATION SURGERY

Non-Genital Surgery

Non-genital procedures such as breast augmentation and facial feminization surgery can be particularly important interventions for transgender women, making it easier for them to present socially in a female gender role.[15] In fact, Ginsberg et al[16] found that facial procedures, including permanent hair removal and facial feminization surgery, were a priority over chest or genital surgery for most transgender women.

Facial Feminization, Thyroid Chondroplasty, and Voice Modification Surgery

Testosterone therapy can dramatically masculinize transgender men by leading to growth of facial and body hair, lowering vocal pitch, and increasing muscle mass. Unfortunately, feminizing hormone therapy does not alter the physical appearance of transgender women to nearly the same degree. As a result, facial feminization procedures are popular among transgender women and can include a combination of jaw and forehead contouring, rhinoplasty, chin reconstruction, scalp advancement, hair transplantation, and dermal filler injections.[17] Vocal cord surgery raises vocal pitch to traditionally feminine ranges and is usually performed with thyroid chondroplasty to reduce the thyroid cartilage (Adam's apple).[15]

Breast Surgery

Breast augmentation has been shown to increase feelings of femininity in transgender women.[17] Natural breast tissue optimizes the cosmetic result of breast augmentation, so the WPATH recommends patients be treated with a minimum of 12 months of feminizing hormone therapy before surgery.[1] Hormone therapy leads to variable breast growth. After 12 to 24 months of treatment many patients experience enough breast development that they choose to forgo augmentation.[1] Augmentation mammoplasty is performed using similar approaches as those used for ciswomen with a few additional considerations. The male chest is broad with a lower and more widely spaced nipple-areolar complex, so patients should be advised that these anatomic factors can limit implant choice. Achieving significant cleavage (medial breast fullness) is difficult because the implant must be centered under the nipple. Lipofilling (fat grafting) can be used for touchups and for primary breast enhancement when only a small augmentation is necessary.[17] The long-term outcomes and safety of lipofilling have not been studied in the transgender population.

Genital Surgery

As part of their gender transition, some transgender women elect to undergo genital GCS. Feminizing genitoplasty should be tailored to meet each patient's goals for her gender identity. At a minimum this involves bilateral orchiectomy to eliminate their major source of endogenous testosterone and decrease postoperative antiandrogen medication requirements. Full genital reconstruction with penectomy, urethroplasty, and vaginoplasty with clitoro-labioplasty represents the opposite end of the spectrum and aims to create a natural-appearing vulva, a neovagina with adequate width and depth for penetrative intercourse, and a sensate neoclitoris.[1,15,18,19] "Zero-depth" vaginoplasty (vulvoplasty with clitoro-labioplasty) is a good option for patients who are interested in having a feminine vulva and clitoris but who do not desire penetrative intercourse and/or want to avoid postoperative neovaginal dilation.

VAGINOPLASTY

Vaginoplasty techniques used during GCS have been adapted from procedures that were originally developed to treat vaginal agenesis.[19] Surgical creation of a neovagina has been described using different skin grafts, intestinal transposition, and pedicled genital or non-genital skin flaps. The optimal vaginoplasty approach has not been determined because large empiric studies directly comparing different procedures have not been performed. Nevertheless, PIV using a pedicled penoscrotal skin flap has emerged as the 1st-line approach for primary vaginoplasty according to most GCS surgeons including the authors whose surgical technique is described in Appendix A.[1,15,19]

Preoperative Considerations

General Considerations

Prospective surgical patients who have met WPATH SOC eligibility criteria should undergo a preoperative evaluation to assess their medical history, identify perioperative risk factors, and complete relevant diagnostic and laboratory testing.[20] Medical conditions should be reasonably well controlled. To optimize wound healing, diabetics should have well-controlled blood glucose with a hemoglobin A_{1c} level below 7%.[21] Smokers should quit at least 6 weeks before surgery; some surgeons perform preoperative urine cotinine testing as confirmation.[21] For any vaginoplasty procedure, prophylactic parenteral antibiotics appropriate for colorectal procedures should be administered within 60 minutes of incision.[22]

Table 2. Permanent hair removal for gender-confirmation surgery[23]

Electrolysis	Laser therapy
Mechanism of action	
An electrical current is transmitted through a small needle or probe to each hair follicle, permanently destroying it.	Laser light energy is absorbed by melanin in the hair shaft, damaging its follicle and decreasing the amount of hair that will grow. Different lasers are used based on hair color and skin type.
Advantages	
Hair follicles can be permanently destroyed	60× faster than electrolysis
Effective for light-colored hair	Requires fewer treatments
Each session less expensive	3–6× short sessions are repeated every 6 wk and completed 3 mo before surgery
	Large surface area treated each session
	Less painful, can pretreat with topical anesthetic
	Efficacy increased by shaving before treatment
	Very effective for dark-colored hair on light skin
Disadvantages	
Much slower than laser hair removal	Hair follicle is not permanently destroyed
Hair follicles are treated individually	Each session more expensive
Sessions last several hours and must be repeated every 1–2 wk for up to 1 y for full results	Not effective for light-colored hair
Results are highly variable and depend on the modality and operator	Must stop any hair removal (waxing, plucking, electrolysis) that damages the bulb for 4 wk before treatment
Painful, requires injected or topical anesthetic	Must strictly avoid sun exposure for ≥6 wk before and after treatment or risk dyspigmentation

Hair Removal

Permanent epilation of the external genitalia with laser therapy or electrolysis is strongly recommended to avoid lining the neovagina with hair-bearing skin, an outcome associated with lower patient satisfaction and potential complications.[8,23,24] Laser hair removal is more popular than electrolysis, but neither method permanently removes all hair and each is associated with advantages and disadvantages (Table 2).[23] There is some evidence that hair follicles regress over time, which could explain why regrowth after laser therapy or electrolysis tends to be sparse.[8,23] Hair removal can take 3 to 6 months and should be completed at least 2 weeks before vaginoplasty.[25]

Individual surgeons undoubtedly have their own protocols for hair removal, but few have been published in the literature. Hair should be removed from the entire penis and perineum plus any scrotal skin that will be used to line the neovaginal vault. This usually involves epilating the entire scrotum but hair removal from a midline strip of scrotal skin (4–10 cm) alone could be sufficient in certain situations.[23,26] Zhang et al[23] recommended patients bring photographs or diagrams from their surgeons that outline areas of hair needing removal to treatment sessions.

Some surgeons have advocated epilation at the time of surgery by aggressively thinning skin flaps to remove deep hair follicles. This practice has not been well studied, but 1st principle reasoning dictates that thinning a skin flap to the point of functioning like a full-thickness skin graft necessarily compromises its blood supply and could increase the risk of wound complications. Furthermore, in the event a rectal perforation occurs during dissection of the neovaginal space, covering the repair with a well-vascularized skin flap is undoubtedly preferable to a poorly vascularized skin graft. Despite the time and expense required for preoperative hair removal, most GCS surgeons believe it adds a margin of safety and insist on its completion before surgery.

Bowel Preparation

A mechanical bowel preparation is recommended for all patients undergoing vaginoplasty. A bowel preparation increases the chance a rectal injury will heal after being repaired primarily instead of requiring a bowel diversion.[17,19,27,28]

Minimize Thromboembolic Risk

Estrogen is associated with an increased risk of thromboembolic events so most centers require it to be discontinued perioperatively, usually for at least 2 weeks before and 2 weeks after surgery.[1,18] Patients should be informed that they might experience hot flashes or mood swings during this time.[8] Smoking further increases the risk of venous thromboembolism for patients taking estrogen therapy, another reason patients should be required to quit smoking completely for at least 6 weeks before and after surgery.[1,18] Prophylactic heparin or low-molecular-weight heparin and pneumatic compression devices also are used intraoperatively and postoperatively by many surgeons.

Skin Graft Vaginoplasty

There are reports of vaginoplasty using genital or non-genital full- or split-thickness skin grafts to line the neovagina going back to the 1930s.[29] Skin grafts are not limited by a vascular pedicle, which ensures more can always be harvested to line the neovagina completely. The downside of a circumferential skin graft is that contraction leads to a cicatrix of scar tissue and introital or neovaginal stenosis in 33% to 45% of cases.[29,30] Undesirable scarring or hypopigmentation of donor skin sites and the lack of natural neovaginal lubrication are other drawbacks to this approach.[19] Despite their historical significance, primary vaginoplasty exclusively using skin grafts is seldom performed in contemporary practice because of these disadvantages.[30] Skin grafts are frequently used when there is insufficient tissue to create a neovagina with suitable depth for penetration from inversion of the penile skin alone.[19,31]

Intestinal Transposition Vaginoplasty

Pedicled rectosigmoid or ileal segments can be isolated through an open or minimally invasive approach, brought into the neovaginal space, and anastomosed with perineal skin create a functional neovagina.[15,17,30] Owing to the intrinsic properties of bowel mucosa, intestinal vaginoplasty produces a neovagina that has ample width and depth, is naturally lubricated with a texture similar to a biologic vagina, and requires less postoperative dilation to maintain its dimensions.[3,27] The benefits of intestinal vaginoplasty are mirrored by encouraging outcomes across functional, esthetic, and QOL measures.[32] Based on published data, intestinal vaginoplasty does not appear inferior to PIV in outcomes or complication rates.[30] Nevertheless, PIV remains the preferred approach for primary vaginoplasty for most GCS surgeons because intestinal transposition inherently involves an intra-abdominal operation and bowel anastomosis. Young transgender patients with penoscrotal hypoplasia after hormone-induced pubertal suppression are a notable exception. These patients might be ideal candidates for primary intestinal vaginoplasty because they have insufficient penoscrotal skin for PIV.[15] Intestinal vaginoplasty also is the preferred approach for salvage cases requiring secondary vaginoplasty.

The most commonly reported complication of intestinal vaginoplasty is introital stenosis, affecting 1.2% to 8.6% of patients.[15,30] Many cases can be treated with neovaginal dilation, although revision surgery might be required.[30] Excessive neovaginal discharge rarely lasts longer than 6 months but can be accompanied by malodor after up to 10% of rectosigmoid vaginoplasties.[27] Bowel complications, including diversion colitis, bowel obstruction, peritonitis, and adenocarcinomas, have been reported but are relatively uncommon.[27,30]

Penile Inversion Vaginoplasty

During PIV an anteriorly based inverted penile skin flap is combined with a 2nd posteriorly based perineal skin flap, which are primarily vascularized by internal pudendal artery branches, and used as a skin tube to line the neovagina.[33,34] PIV has many advantages and is the preferred approach for primary vaginoplasty in most scenarios. Penile skin is smooth, elastic, largely non-hair bearing, and contains minimal connective tissue.[15] Vascularized flaps are less likely to contract than skin grafts, so rates of neovaginal stricture and introital stenosis are lower and range from 1% to 12% and 2.5% to 15%, respectively.[15,17,21,30] Unlike intestinal transposition vaginoplasty, PIV does not require an intra-abdominal operation or bowel resection and eliminates the risk of malodorous neovaginal discharge, although it does require more postoperative dilation.[19]

The primary disadvantage of PIV is that there is a finite amount of penile skin to line the neovagina. Fortunately, the flap can easily be augmented with full-thickness skin grafts harvested from redundant scrotal skin excised during labioplasty, non-genital split-thickness skin grafts, or urethral flaps to create a neovagina of adequate depth.[30]

Clitoroplasty

The goal of clitoroplasty is the creation of an esthetically appealing neoclitoris with preserved erogenous sensitivity.[35] Several successful clitoroplasty techniques have been described, all using a vascularized segment of the dorsal glans penis innervated by the dorsal neurovascular bundle.[28] More than 80% of transgender women can achieve orgasm after clitoroplasty (range = 29–100%).[2,8,24,30,35–37]

Vulvoplasty

The labia majora and minora and clitoral hood are created during vulvoplasty. Labioplasty using a straightforward scrotal rearrangement yields the labia majora, its female embryologic equivalent, with excellent esthetic results. Labioplasty to create a feminine vulva can be performed in isolation for patients who do not desire a functional neovagina.[17] By contrast, creation of the labia minora has posed a challenge for surgeons. Its embryologic equivalent, the penile urethra, is amputated during penectomy so it cannot be used for reconstruction.[38] Several techniques to construct the labia minora have been described, with many surgeons gravitating toward the use of a penile shaft skin, a tradeoff that leaves less skin available to line the neovagina during PIV.[19,28,36,39–41] Penile shaft skin also is often used to create the clitoral hood in circumcised patients, in exchange for lining the neovagina. In uncircumcised patients, the prepuce can be used to form the clitoral hood, its female corollary.[38]

VAGINOPLASTY COMPLICATIONS

All major surgeries carry a risk of complications and feminizing GCS is no exception. Vaginoplasty requires disassembly, rearrangement, and reconstruction of multiple organ systems and thus is inherently associated with a diverse complication profile (Table 3). Patients considering vaginoplasty should understand

Table 3. Relative frequency of vaginoplasty complications[3,21,26,27,30,32,41–43]

	Frequency	Notes
Major systemic complications		
PE or DVT	<1%	
Stroke	Very rare	
Death	Very rare	
Genital complications		
Introital stenosis	Up to 15%	Increased risk if non-compliant with neovaginal dilation or sexually inactive
Neovaginal stenosis	<10%	Prevented and treated with neovaginal dilation
Malodorous discharge	<10%	Intestinal vaginoplasty, especially rectosigmoid
Neovaginal prolapse	<10%	Presents when neovaginal stent is removed; treat by reinsertion ± fibrin glue, bedrest; mucosal prolapse can be excised, secondary vaginopexy rarely necessary
Neovaginal mucosal bleeding	<10%	Intestinal vaginoplasty, especially rectosigmoid
Dyspareunia	<5%	Transient, lasting <6 mo
Neovaginal necrosis	<5%	Usually minor, after piv
Labial necrosis	<5%	Usually minor
Clitoral necrosis	<5%	Usually minor, erogenous sensation remains intact
Introital atresia	<3%	Treat with introitoplasty
Neovaginal atresia	<1%	Treat with secondary intestinal vaginoplasty
Rectovaginal fistula	<1%	Increased risk after rectal injury, secondary vaginoplasty
Neovaginal perforation	Very rare	
Urinary complications		
Misdirected urinary stream	Up to 40%	Tends to spray upward, treat with ventral meatoplasty
LUTS	Up to 20%	Most commonly urgency, frequency, and weak stream
Urinary incontinence	Up to 20%	Stress, urge, or mixed
Urinary retention	<15%	Postoperative and transient
Meatal stenosis	<10%	Treated with meatoplasty
Urethral injury	<5%	Intraoperative, can repair primarily + catheter drainage
Urinary tract infection	<5%	
Urethrovaginal fistula	<1%	Presents with continuous incontinence, recurrent UTI
Urethral necrosis	<1%	
Urethral prolapse	Very rare	
Wound complications		
Wound healing disorders	Up to 30%	Dehiscence, minor necrosis, or delayed wound healing; most are treated conservatively
Infection	Up to 20%	Increased risk with DM, history of drug use, anticoagulation
Unesthetic scar	Very rare	
Bleeding complications		
Postoperative hemorrhage	<10%	Most from corpus spongiosum; treat with placement of 22-Fr catheter or hemostatic suture placement (1–2%)
Blood transfusions	<5%	
Hematoma	<5%	Decreased risk with postoperative pressure dressing; can predispose for wound dehiscence; treat with expectant management, surgical intervention rarely required
Gastrointestinal complications		
Rectal injury (intraoperative)	<5%	Treat most with primary repair and low residue diet; bowel diversion rarely required
Ileus	<5%	
Peritonitis	<5%	
Bowel obstruction	<1%	50% will require bowel resection or lysis of adhesions
Diversion colitis	Very rare	
Neovaginal adenocarcinoma	Very rare	After intestinal vaginoplasty

DM = diabetes mellitus; DVT = deep vein thrombosis; LUTS = lower urinary tract symptoms; PE = pulmonary embolism; PIV = penile inversion vaginoplasty; UTI = urinary tract infection.

that complications are common. Life-threatening adverse events are rare and the risk of mortality is virtually 0%.[1,14,21] Patients also should be aware that 25% to 80% of patients undergo secondary procedures to optimize voiding or for vulvar cosmesis after vaginoplasty.[2,8,24,30,32,35–37] In this review the authors highlight certain common and/or major complications.

Intraoperative Complications

Serious intraoperative complications are uncommon. Rectal injuries sustained during dissection of the neovaginal space are the most frequently reported (0.45–4.5%).[21,30,41,42] Most can be repaired primarily with a 2-layer closure using absorbable suture. Bowel diversion is rarely necessary.[26] Most patients who sustain a rectal injury do not develop any long-term sequelae, although they are at greater risk of developing a rectovaginal fistula.[21,30,44] Urethral injuries occur in 0% to 4.0% of cases and can be repaired primarily with absorbable suture and prolonged catheter drainage.[21,30,45] Most groups report sporadic intraoperative hemorrhage requiring blood transfusions.[21,27,30,42]

Postoperative Complications

Genital Complications

A modest percentage of patients are affected by stenosis of their introitus (mean = 12%, range = 1.2–15%) or neovagina (mean = 7%, range = 1–12%) after vaginoplasty.[21,27,30,42,43] A regimen of postoperative prophylactic dilation is crucial to minimize the development of these outcomes including their worst iterations, complete atresia of the introitus or entire neovagina. Stenosis is often treated with dilation. Minor surgical revision with U-shaped introitoplasty or relaxing incisions could be necessary for recalcitrant cases.[27] Complete neovaginal atresia is very rare and requires a secondary intestinal vaginoplasty.

Rectovaginal fistulas represent the other end of the spectrum of vaginoplasty complications. They complicate only approximately 1% (range = 0–17%) of cases but represent a distressing outcome for patients and their surgeons.[8,30,44] In the largest published series of neovaginal fistulas in transgender women after GCS, van der Sluis et al[44] investigated the characteristics of 13 rectovaginal fistulas in a cohort of 1,082 patients. Every patient presented with foul-smelling discharge or passage of flatus and/or feces from her neovagina, often immediately after removing the neovaginal stent placed during surgery. They identified several factors associated with rectovaginal fistula development. Rectal injuries were an expected culprit because they compromise rectal wall integrity. Fistulas also were more common after revision vaginoplasty (6.3%) compared with primary intestinal vaginoplasty (0%) or PIV (0.8%) or when the postoperative course was complicated by hematoma, abscess, or flap necrosis.[44] These findings could support a theory proposed by Selvaggi and Bellringer[15] that the anterior rectal wall can be devascularized during dissection of the neovaginal space, compromising the tissue and lowering the threshold for a fistula to develop. Resolution of a rectovaginal fistula usually requires surgery, including fistulectomy with primary repair, the use of local advancement flaps, or, less commonly, bowel diversion.[44] Small fistulas can resolve with conservative management including a low residue diet.

Extensive necrosis of the neovagina, labia, or neoclitoris can occur but is infrequent because pelvic structures are generously vascularized. Minor wound dehiscence is known to be extremely common in the immediate postoperative period and is likely under-reported in the literature. Minor tissue necrosis can be managed conservatively with local wound care. Surgical debridement is rarely necessary.[28] Erogenous sensation is usually conserved after partial neoclitoral necrosis because it revascularizes with time. Orgasm might be possible after neoclitoral necrosis with complete neurovascular loss by stimulating the prostate and residual erectile tissue within the corpus spongiosum.[28]

Urinary Complications

A misdirected urinary stream is the most common urinary side effect of vaginoplasty, affecting 5.6% to 33% of patients.[8,21,24,30] Meatal stenosis presents with a spraying urinary stream, obstructive voiding symptoms, or urinary retention and can be corrected with a simple meatoplasty, rearranging tissue as necessary to produce a patent, unobstructed meatus. Perioperative urinary retention is temporary and treated by replacing a urethral catheter or placing a suprapubic tube.[21] After vaginoplasty a small percentage of patients develop transient or persistent urinary incontinence (stress, urge, or mixed) or other lower urinary tract symptoms.[1,46,47] Neither the internal nor the external urinary sphincter is directly compromised during vaginoplasty, so 1 theory is that stress incontinence results from damage to the external sphincter complex during dissection of the neovaginal space.[46] The authors postulate that urinary symptoms also could be affected by a positional change in the bladder, underlying detrusor overactivity that is unmasked when the urethra is shortened, or development of periurethral fibrosis.

Hematologic Complications

Venous thromboembolic events are a feared complication of vaginoplasty because several hours of surgery are performed with the patient in lithotomy and followed by several days of decreased ambulation. Because of thrombosis prophylaxis strategies, including unfractionated or low-molecular-weight heparin, pneumatic compression stockings, discontinuing estrogen therapy perioperatively, and encouraging smoking cessation, the risk of venous thromboembolic events has been decreased to less than 1%.[3,15,21,24,26,30]

Clinically significant bleeding occurs in 1.7% to 10% of cases and commonly arises from the corpus spongiosum.[15,21,26,30,41] Fewer than 5% of patients require blood transfusions.[21,26,27,40–42,45] A perineal pressure dressing applied at the completion of surgery helps avoid postoperative hemorrhage. Large labial hematomas should be drained to prevent abscess formation and wound dehiscence.[15]

SEXUAL FUNCTION AFTER VAGINOPLASTY

Human sexual function is incompletely understood and complex and affected by countless organic and external factors. As a result, objectively defining what constitutes satisfactory sexual function can be problematic. The goal of feminizing GCS is to create a neovagina with sexual function that mirrors that of a biologic woman with adequate dimensions for penetrative intercourse, a sensate neoclitoris capable of sexual arousal and orgasm, and a cosmetically feminine vulva. Postoperative patient satisfaction is high for many, but not all, of these objectives.[3,8,27] Surgeons should discuss these limitations with patients and provide them with realistic expectations for postoperative sexual function. The optimal vaginoplasty technique with regard to sexual function outcomes has not been determined, although based on available data no approach appears obviously inferior. Referral to a pelvic floor physical therapist can aid in recovery and improve sexual functioning after vaginoplasty.

Areas of Higher Patient Satisfaction

Overall Sexual Function

Most patients are sexually active (mean = 71%, range = 33–89%) and subjectively satisfied with their sexual function after feminizing vaginoplasty.[3,27,30–32] Hess et al[2] found that 91.4% of patients who responded to a questionnaire were very satisfied (34.4%), satisfied (37.6%), or mostly satisfied (19.4%) with their sexual function after PIV. 2 studies of patients who had undergone intestinal vaginoplasty yielded similar results. Patients rated their neovaginal sexual function after primary and secondary intestinal vaginoplasty with an average score of 8.0 (range = 1–10) and 7.3 ± 1.8 (range = 1–10), respectively.[3,32] The generally high scores described in these studies are interesting to consider in the context of other measures used to report sexual function after vaginoplasty. For example, the Female Sexual Function Index (FSFI) is a validated questionnaire used to assess female sexual function; a score lower than 26.55 is considered the cutoff for sexual dysfunction.[48,49] The same transgender women who subjectively rate their sexual function favorably after vaginoplasty have FSFI scores that are consistently below the 26.55 threshold (Table 4).[3,31,32] This discordance suggests that traditional measures of female sexual function, such as the FSFI, which was validated in a cohort of biologic women who were sexually active on a regular basis within stable heterosexual relationships, should be taken with a grain of salt when applied to transgender women after vaginoplasty.

Vaginal Dimensions

Having the deepest feasible neovagina is a major concern for many patients.[28] To accommodate penetration comfortably, neovaginal width and depth should be at least 3 and 10 cm, respectively.[17] These dimensions can almost always be achieved during vaginoplasty. To maintain neovaginal size, regular dilation or penetrative intercourse is critical, especially in the 1st postoperative year.[1] Fortunately, 76% to 100% of patients are satisfied with their neovaginal depth for intercourse.[3,30,31,41] Reports of secondary procedures to increase neovaginal depth are uncommon.

Orgasm

The ability to reach orgasm is another important measure of sexual function after feminizing GCS. As the surgical technique for clitoroplasty has been refined, rates of orgasm have increased and are generally higher than 80% in contemporary studies (range = 29–100%).[2,8,24,30,32,35–37] Interestingly, 25% to 46.9% of patients report improved orgasms after vaginoplasty.[31,32]

Cosmesis

78% to 100% of patients are satisfied with the esthetic outcome of surgery.[2,31,32,41] Vaginoplasty patients graded the appearance of their genitals with an average score of 7.9 ± 1.5 (range = 4–10) in 1 study.[31] In fact, the vaginoplasty cohort scored higher than biologic women on most domains of the Female Genital Self-Imaging Scale, including for the questions "I feel positively about my genitals" and "I am satisfied with my appearance of my genitals."[31] Bouman et al[32] reported patients' median score for their esthetic outcome after intestinal vaginoplasty was 8.0 (range = 3–10). In another study of 94 vaginoplasty patients, only 2 reported being dissatisfied and 1 reported being very dissatisfied with the appearance of their genitals after surgery.[2] The positive perception most patients have about their esthetic appearance after vaginoplasty is encouraging, but there is still opportunity for improvement because a reported 25% to 80% of patients undergo secondary cosmetic procedures, usually minor labioplasty, after vaginoplasty.[3,21,26,30,43]

Areas of Lower Patient Satisfaction

Lubrication

Most vaginoplasty patients will require additional lubrication for sexual intercourse.[5,8,17,35,50] In biologic women sexual

Table 4. Sexual function after vaginoplasty[3,21,32]

	Penile inversion vaginoplasty	Primary intestinal vaginoplasty	Secondary intestinal vaginoplasty
Patient's subjective sexual function rating	Mean 7.7 ± 1.9 (1–10)	Median 8.0 (1–10)	Mean 7.3 ± 1.8 (1–10)
Female Sexual Function Index score	18.7 ± 10.8	17.5 ± 11.5	24.0 ± 10.8

arousal leads to pelvic vasocongestion and transudation of interstitial fluid through epithelial cells lining the vagina. This fluid lubricates the vaginal mucosa, protecting it from friction-related injuries and pain during penetration.[51] By contrast, a neovagina lined with keratinized penoscrotal skin cells typically does not become lubricated to the same degree. Buncamper et al[31] found the mean FSFI score for vaginal lubrication after PIV in 49 patients was 2.8 ± 2.4. When only sexually active patients in the cohort were considered, the mean FSFI lubrication score increased to 3.9 ± 1.9. An advantage of intestinal vaginoplasty is that bowel mucosa is self-lubricating, a property that was reflected in FSFI lubrication scores that increased to 4.0 ± 2.6. All vaginoplasty scores were still well below of the average FSFI lubrication score for biologic women (5.7 ± 1.0).[31,32]

Dyspareunia

Rates of dyspareunia vary widely in the literature, from 0% to 24.7%.[27,30] Mean reported FSFI scores for comfort during intercourse after PIV (2.2 ± 2.7), primary intestinal vaginoplasty (2.0 ± 2.1), and secondary vaginoplasty (3.5 ± 2.2) are lower than those of biologic women with normal sexual function (5.7 ± 0.8).[3,31,32]

CONCLUSION

Comprehensive gender dysphoria treatment often requires GCS in addition to cross-sex hormone therapy, social gender transition, and psychotherapy. GCS alleviates gender dysphoria and improves the lives of appropriately selected patients. This article is the 2nd in a 3-part series. Part 1 included a review of the non-operative management of gender dysphoria.[4] In this section, the authors outlined surgical eligibility criteria, factors associated with regret, and the ways transgender men and women benefit from GCS before focusing on feminizing vaginoplasty including a description of the authors' technique for PIV. Most GCS surgeons have gravitated toward using PIV for primary procedures and intestinal vaginoplasty for secondary procedures. The 2 techniques are safe and associated with high patient satisfaction with postoperative sexual function. Part 3 emphasizes masculinizing GCS and a discussion of the ancillary procedures and services used to treat gender dysphoria.

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REFERENCES

1. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgend 2012; 13:165-232.
2. Hess J, Rossi Neto R, Panic L, et al. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int 2014; 111:795-801.
3. van der Sluis WB, Bouman M-B, de Boer NKH, et al. Long-term follow-up of transgender women after secondary intestinal vaginoplasty. J Sex Med 2016;13:702-710.
4. Hadj-Moussa M, Ohl DA, Kuzon WM. Evaluation and treatment of gender dysphoria to prepare for gender confirmation surgery. Sex Med Rev 2017.
5. De Cuypere G, T'Sjoen G, Beerten R, et al. Sexual and physical health after sex reassignment surgery. Arch Sex Behav 2005; 34:679-690.
6. de Vries A, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696-704.
7. Cardoso da Silva D, Schwarz K, Fontanari AMV, et al. WHOQOL-100 before and after sex reassignment surgery in Brazilian male-to-female transsexual individuals. J Sex Med 2016;13:988-993.
8. Lawrence AA. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav 2006;35:717-727.
9. Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav 2015;44:1321-1329.
10. Löwenberg H, Lax H, Rossi Neto R, et al. Komplikationen, subjektive Zufriedenheit und sexuelles Erleben nach geschlechtsangleichender Operation bei Mann-zu-Frau-Transsexualität. Zeitschr Sex 2010;23:328-347.
11. Gooren LJ. Care of transsexual persons. N Engl J Med 2011; 364:2559-2560; author reply 2560.
12. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 2003;32:299-315.
13. Landén M, Wålinder J, Hambert G, et al. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand 1998; 97:284-289.

14. Djordjevic ML, Bizic MR, Duisin D, et al. Reversal surgery in regretful male-to-female transsexuals after sex reassignment surgery. J Sex Med 2016;13:1000-1007.
15. Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. Nat Rev Urol 2011;8:274-282.
16. Ginsberg BA, Calderon M, Seminara NM, et al. A potential role for the dermatologist in the physical transformation of transgender people: a survey of attitudes and practices within the transgender community. J Am Acad Dermatol 2016; 74:303-308.
17. Colebunders B, Brondeel S, D'Arpa S, et al. An update on the surgical treatment for transgender patients. Sex Med Rev 2017;5:103-109.
18. Wilczynski C, Emanuele MA. Treating a transgender patient: overview of the guidelines. Postgrad Med 2014;126:121-128.
19. Schechter LS. 15—Surgery for gender identity disorder. 3rd ed. Philadelphia: Elsevier; 2013.
20. Wijeysundera DN, Sweitzer B-J. Preoperative evaluation. In: Miller, ed. Miller's anesthesia. 8th ed. Philadelphia: Elsevier; 2015. p. 1085-1155.
21. Buncamper ME, van der Sluis WB, van der Pas RSD, et al. Surgical outcome after penile inversion vaginoplasty: a retrospective study of 475 transgender women. Plast Reconstr Surg 2016;138:999-1007.
22. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Heal Pharm 2013;70:195-283.
23. Zhang WR, Garrett GL, Arron ST, et al. Laser hair removal for genital gender affirming surgery. Transl Androl Urol 2016; 5:381-387.
24. Goddard JC, Vickery RM, Qureshi A, et al. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. BJU Int 2007;100:607-613.
25. Schechter L. Surgical management of the transgender patient. 1st ed. Philadelphia: Elsevier; 2017.
26. Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. Semin Plast Surg 2011;25:163-174.
27. Bouman MB, van Zeijl MCT, Buncamper ME, et al. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. J Sex Med 2014;11:1835-1847.
28. Trombetta C, Bertolotto M, Liguori G, eds. Management of gender dysphoria. 1st ed. Milan: Springer Milan; 2015.
29. Selvaggi G, Ceulemans P, De Cuypere G, et al. Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. Plast Reconstr Surg 2005;116:135e-145e.
30. Horbach SER, Bouman M-B, Smit JM, et al. Outcome of vaginoplasty in male-to-female transgenders: a systematic review of surgical techniques. J Sex Med 2015;12:1499-1512.
31. Buncamper ME, Honselaar JS, Bouman MB, et al. Aesthetic and functional outcomes of neovaginoplasty using penile skin in male-to-female transsexuals. J Sex Med 2015;12: 1626-1634.
32. Bouman MB, van der Sluis WB, van Woudenberg Hamstra LE, et al. Patient-reported esthetic and functional outcomes of primary total laparoscopic intestinal vaginoplasty in transgender women with penoscrotal hypoplasia. J Sex Med 2016; 13:1438-1444.
33. Dwyer ME, Salgado CJ, Lightner DJ. Normal penile, scrotal, and perineal anatomy with reconstructive considerations. Semin Plast Surg 2011;25:179-188.
34. Giraldo F, Mora MJ, Solano A, et al. Male perineogenital anatomy and clinical applications in genital reconstructions and male-to-female sex reassignment surgery. Plast Reconstr Surg 2002;109:1301-1310.
35. LeBreton M, Courtois F, Journel NM, et al. Genital sensory detection thresholds and patient satisfaction with vaginoplasty in male-to-female transgender women. J Sex Med 2017; 14:274-281.
36. Perovic SV, Stanojevic DS, Djordjevic MLJ. Vaginoplasty in male transsexuals using penile skin and a urethral flap. BJU Int 2000;86:843-850.
37. Wagner S, Greco F, Hoda MR, et al. Male-to-female transsexualism: technique, results and 3-year follow-up in 50 patients. Urol Int 2010;84:330-333.
38. Park JM. Embryology of the genitourinary tract. In: Wein, ed. 11th ed. Philadelphia: Elsevier; 2016. p. 2823-2848.e4.
39. Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. Curr Opin Endocrinol Diabetes Obes 2013;20:570-574.
40. Wangjiraniran B, Selvaggi G, Chokrungvaranont P, et al. Male-to-female vaginoplasty: Preecha's surgical technique. J Plast Surg Hand Surg 2015;49:153-159.
41. Amend B, Seibold J, Toomey P, et al. Surgical reconstruction for male-to-female sex reassignment. Eur Urol 2013;64: 141-149.
42. Falcone M, Timpano M, Ceruti C, et al. A single-center analysis on the learning curve of male-to-female penoscrotal vaginoplasty by multiple surgical measures. Urology 2017; 99:234-239.
43. Raigosa M, Avvedimento S, Yoon TS, et al. Male-to-female genital reassignment surgery: a retrospective review of surgical technique and complications in 60 patients. J Sex Med 2015;12:1837-1845.
44. van der Sluis WB, Bouman M-B, Buncamper ME, et al. Clinical characteristics and management of neovaginal fistulas after vaginoplasty in transgender women. Obstet Gynecol 2016; 127:1118-1126.
45. Neto RR, Hintz F, Krege S, et al. Gender reassignment surgery—a 13 year review of surgical outcomes. Int Braz J Urol 2012;38:97-107.
46. Hoebeke P, Selvaggi G, Ceulemans P, et al. Impact of sex reassignment surgery on lower urinary tract function. Eur Urol 2005;47:398-402.
47. Melloni C, Melloni G, Rossi M, et al. Lower urinary tract symptoms in male-to-female transsexuals. Plast Reconstr Surg Global Open 2016;4:e655.

48. Rosen C, Brown J, Heiman S, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191.

49. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1-20.

50. Alessandrescu D, Peltecu GC, Buhimschi CS, et al. Neocolpopoiesis with split-thickness skin graft as a surgical treatment of vaginal agenesis: retrospective review of 201 cases. Am J Obstet Gynecol 1996;175:131-138.

51. Dawson SJ, Sawatsky ML, Lalumière ML. Assessment of introital lubrication. Arch Sex Behav 2015;44:1527-1535.

Appendix A. Surgical procedure for penile inversion vaginoplasty

- Positioning and patient preparation
  - Patient is positioned in lithotomy. SCDs and SQH 5,000 U are given for thrombosis prophylaxis. IV prophylactic antibiotics are administered. Surgical field is prepared with a povidone-iodine solution from the umbilicus to the knees, including the buttocks. A urethral catheter is placed.
- Harvest skin flaps and grafts
  - Posteriorly based perineal skin flap
    - Starting 2 cm above the anus, mark and raise a trapezoidal perineal skin flap with a 3.5- to 4-cm-wide base, tapering to 3.0- to 3.5-cm wide where the perineum meets the scrotum. The flap's vertical distance is variable, depending on length of the patient's perineum.
  - Full-thickness scrotal skin graft
    - A 10-cm-wide × 5-cm-long rectangle of scrotal skin abutting the superior border of the perineal skin flap is raised sharply. On the back table, the scrotal skin graft is aggressively defatted and shaped around a vaginal stent to form the neovaginal apex.
  - Anteriorly based penile skin flap
    - A vertical incision is extended ventrally along the midline raphae from the superior edge of the scrotal skin flap to the mid-shaft of the penis, leaving a few centimeters of an intact circumferential skin tube around the distal aspect of the penis.
- Develop neovaginal space
  - Develop ischioanal fossae
    - The bulbospongiosus' attachments to the perineal body are divided, mobilizing the urethra. To access the ischioanal fossae, the perineal membrane is nicked to the right and left of the perineal body and the space is bluntly dissected. Bilateral superficial perineal muscles traveling horizontally and inserting into the perineal body are isolated, ligated by suture, and divided.
  - Develop rectovesical space
    - While applying gentle downward traction on the rectum, sharply divide the rectourethralis, which tents the anterior wall of the rectum to the apex of the perineal body, and fibers from the membranous urethra. Dissection proceeds sharply using the Foley catheter as a guide until the apex of the prostate is palpated. Then, blunt dissection is carried out along a relatively avascular perirectal fat plane anterior to the Denonvilliers rectoprostatic fascia, which remains draped over the rectum. The Denonvilliers fascia has attachments at the base of the prostate that might need to be sharply divided so the dissection can be carried out to the level of the peritoneal reflection. The authors do not routinely incise the levator muscles to widen the neovaginal space.
    - Check for a rectal injury by placing a clean lap sponge in the neovaginal space and instilling 50% povidone-iodine solution 60 mL into the rectum. A rectal injury has occurred if any povidone-iodine is seen on the lap sponge when it is removed from the neovaginal space. A bimanual examination with 1 finger in the rectum and another in the neovaginal space also confirms intact rectal mucosa.
- Bilateral orchiectomy
  - Each spermatic cord is ligated by suture at the level of the external inguinal ring so the stumps retract into the inguinal canal and are not palpable in the groin.
- Deglove penis and release attachments
  - Mark and incise a circumferential incision approximately 3 cm from the corona. Deglove the penis, leaving the Buck fascia intact. The distal penile shaft skin will be used to construct the clitoral hood and labia minora. Remaining close to the inferior pubic ramus, divide the fundiform and deep suspensory ligaments on the dorsal aspect of the penis. The decussation of the crura is visible once the suspensory ligament is divided.
- Raise the dorsal neurovascular bundle and neoclitoris
  - Starting on the lateral aspect of each corporal body, develop a plane between the Buck fascia and the tunica albuginea and raise the dorsal NVB. Carry the dissection proximally until the NVB is released from the corpora as it decussates and distally to the level of the glans. On the dorsal glans, mark a triangle with a 1-cm-wide base at the corona. Incise the glans and dissect deeply to expose the tips of the corpora. Preserve the maximum amount of glanular erectile tissue on the neoclitoris.
- Penile disassembly
  - Separate the corpus spongiosum from the corporal bodies. Amputate each corporal body at the level of the pubis and over-sew to maintain hemostasis.

(continued)

Appendix A. Continued

Prepare the urethra
Resect the bulbospongiosum off the bulbar urethra. Transect the pendulous urethra, leaving adequate length for the dorsal aspect to line the vestibule between the neomeatus and neoclitoris. Excise spongiosum from the ventral aspect of the bulbar urethra to minimize engorgement during sexual arousal, which can cause narrowing of the neovagina and dyspareunia.
Raise suprapubic advancement flap
To minimize upward tension on the penile skin flap positioned within the neovaginal space, it is mobilized by raising an advancement flap from the mons and suprapubic skin. Place 2 closed-suction drains, 1 in the lower abdomen under the advancement flap and the other adjacent to the rectum and neovagina. The neovaginal space drain should be observed carefully for the presence of feculent material, which would indicate a rectal leak.
Position neoclitoris
Tack down tissue surrounding the dorsal NVB underneath the suprapubic advancement flap so that when the NVB is folded toward the perineum, there is no twisting or kinking of its pedicle and the neoclitoris is positioned ~1 cm inferior to the pubic arch.
Labioplasty
Secure skin from each penoscrotal junction to its corresponding corner at the base of the perineal skin flap to form the labia majora. A minor excision of skin is usually necessary to achieve a suitable contour. Close skin edges.
Create window for neoclitoris and neomeatus
Position the invaginated penile skin tube within the neovaginal space. Make a V-shaped incision over the impression made by the neoclitoris under the skin. Extend the window with a vertical incision toward the rectum to accommodate the meatus. Release the penile skin flap and pass the urethra and Foley catheter through the window. Replace the penile skin flap within the neovaginal space.
Clitoroplasty
Use a square stitch on the clitoris' ventral aspect to produce a conical shape. To construct the clitoral hood, suture the distal penile shaft skin to the edges of the clitoral window. The clitoral hood retracts postoperatively to adequately expose the neoclitoris.
Meatoplasty
The urethra is trimmed to a length that reaches the neoclitoris. Suture the distal aspect of the dorsal urethral plate to the posterior margin of the neoclitoris. Spatulate the ventral urethra so the apex of the meatus is positioned 2–3 cm below the neoclitoris and suture an urethrocutaneous anastomosis.
Line neovagina
Inset the trapezoidal perineoscrotal skin flap into a midline incision of the penile skin tube; this serves to widen the neovaginal introitus. If a skin graft is being used to lengthen the neovagina, suture it to the end of the penile skin tube; otherwise, close the apex of the penile skin tube with absorbable suture. Position the tubularized perineoscrotal flap, penile skin flap, and any scrotal skin graft into the neovaginal space. The neovaginal lining should be held in position for 5 days. This can be accomplished with a bolstered vaginal packing (our preference) or with a Silastic neovaginal stent.

SCDs = sequential compression devices; SQH = subcutaneous heparin; IV = intravenous; NVB = neurovascular bundle.

ORIGINAL ARTICLE

Satisfaction With Male-to-Female Gender Reassignment Surgery

Results of a Retrospective Analysis

Jochen Hess, Roberto Rossi Neto, Leo Panic, Herbert Rübben, Wolfgang Senf

SUMMARY

Background: The frequency of gender identity disorder is hard to determine; the number of gender reassignment operations and of court proceedings in accordance with the German Law on Transsexuality almost certainly do not fully reflect the underlying reality. There have been only a few studies on patient satisfaction with male-to-female gender reassignment surgery.

Methods: 254 consecutive patients who had undergone male-to-female gender reassignment surgery at Essen University Hospital's Department of Urology retrospectively filled out a questionnaire about their subjective postoperative satisfaction.

Results: 119 (46.9%) of the patients filled out and returned the questionnaires, at a mean of 5.05 years after surgery (standard deviation 1.61 years, range 1–7 years). 90.2% said their expectations for life as a woman were fulfilled postoperatively. 85.4% saw themselves as women. 61.2% were satisfied, and 26.2% very satisfied, with their outward appearance as a woman; 37.6% were satisfied, and 34.4% very satisfied, with the functional outcome. 65.7% said they were satisfied with their life as it is now.

Conclusion: The very high rates of subjective satisfaction and the surgical outcomes indicate that gender reassignment surgery is beneficial. These findings must be interpreted with caution, however, because fewer than half of the questionnaires were returned.

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Culturally, gender is considered an obvious, unambiguous dichotomy. The term "gender identity" denotes the consistency of one's emotional and cognitive experience of one's own gender and the objective manifestations of a particular gender. In gender identity disorder, one's own anatomical sex is objectively perceived but is felt to be alien, whereas the term "gender incongruence" refers to a difference between an individual's gender identity and prevailing cultural norms. Finally, gender dysphoria is the suffering that results. The treatment guidelines of the World Professional Association of Transgender Health (WPATH) state that gender identity need not coincide with anatomical sex as determined at birth. Transgender identity should therefore be considered neither negative nor pathological (1). Unfortunately, gender incongruence often leads to discrimination against the affected individual, which can favor the development of psychological complaints such as anxiety disorders and depression (2–4). While some transgender individuals are able to realize their gender identity without surgery, for many gender reassignment surgery is an essential, medically necessary step in the treatment of their gender dysphoria (5). Research conducted to date has shown that gender reassignment surgery has a positive effect on subjective wellbeing and sexual function (2, 6, 7). The surgical procedure (penile inversion with sensitive clitoroplasty) is described in *eBox 1*.

Prevalence

No official figures are available on the prevalence of transgender or gender-nonconforming individuals, and it is very difficult to arrive at a realistic estimate. There is no central reporting register in Germany. Furthermore, figures for those who seek medical help for gender dysphoria would in any case give only an imprecise idea of the true prevalence. The global prevalence of transgender individuals has been estimated at approximately 1 per 11 900 to 1 per 45 000 for male-to-female individuals and approximately 1 per 30 400 to 1 per 200 000 for female-to-male individuals (1). Weitze and Osburg estimate prevalence in Germany at 1 per 42 000 (8). In contrast, De Cuypere et al. (9) suppose a prevalence of 1 per 12 900 for [illegible]imate

TABLE 1

Prevalence of transsexualism and ratio of male-to-female to female-to-male cases (by year of publication)

Author	Year	Country	MTF (per 100 000)	FTM (per 100 000)	MTF:FTM ratio (rounded)
Pauly (31)	1968	USA	1.0	0.25	4:1
Walinder (32)	1968	Sweden	2.7	1.0	3:1
Hoenig and Kenna (33)	1974	UK	3.0	0.93	3:1
Ross et al. (34)	1981	Australia	4.2	0.67	6:1
O´Gorman (35)	1982	Ireland	1.9	–	3:1
Tsoi (36)	1988	Singapore	35.1	12.0	3:1
Ekland et al. (37)	1988	Netherlands	18.0	54.0	3:1
van Kesteren et al. (11)	1996	Netherlands	8.8	3.2	3:1
Landén et al. (38)	1996	Sweden	–	–	3:1
Weitze and Osburg (8)	1996	Germany	2.4	1.0	2:1
Wilson et al. (39)	1999	Scotland	13.4	3.2	4:1
Garrels et al. (12)	2000	Germany	–	–	1:1
Haraldsen and Dahl (40)	2000	Norway	–	–	1:1
Olsson and Moller (e1)	2003	Sweden	–	–	2:1
Gomez-Gil et al. (e2)	2006	Spain	4.7	2.1	2:1
de Cuypere et al. (9)	2007	Belgium	7.7	3.0	3:1
Vujovic et al. (e3)	2009	Serbia	0.9	0.9	1:1
Coleman et al. (1)	2012	Global	8.4	2.2	4:1

MTF: male-to-female; FTM: female-to-male

prevalence among US veterans at 1 per 4366. This compares to an estimated prevalence of 1 per 23 255 in the general population. Even if percentages of transgender individuals in different parts of the world are comparable, it is highly likely that cultural differences will lead to differing behavior and expression of gender identity, resulting in differing levels of gender dysphoria (1). The ratio of male-to-female to female-to-male transgender individuals varies greatly. Although it was given as approximately 3:1 by van Kesteren (11), it is 2.3:1 according to Weitze and Osburg (8) and 1.4:1 according to Dhejne (3). Garrels (12) found a gradual decrease in the difference between the two figures in Germany, with the ratio decreasing from 3.5:1 (in the 1950s and 60s) to 1.2:1 (1995 to 1998) *(Table 1)*.

Criteria for diagnosis

Transsexualism is primarily a problem of gender identity (transidentity) or gender role (transgenderism) rather than of sexuality (13). In Germany, it is diagnosed according to ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems).

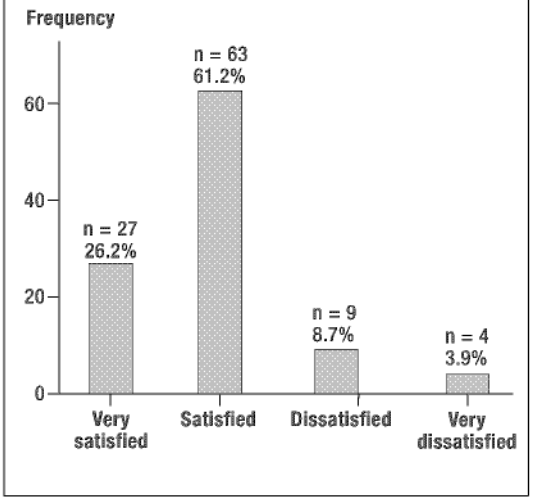
Criteria for diagnosis include the following:

- Feeling of unease or not belonging to biological gender
- Desire to live and be accepted as a member of the opposite sex
- Presence of this desire for at least two years persistently
- Wish for hormonal treatment and surgery
- Not a symptom of another mental disorder
- Not associated with intersex, genetic, or gender chromosomal abnormalities.

Psychological aspects of transsexualism

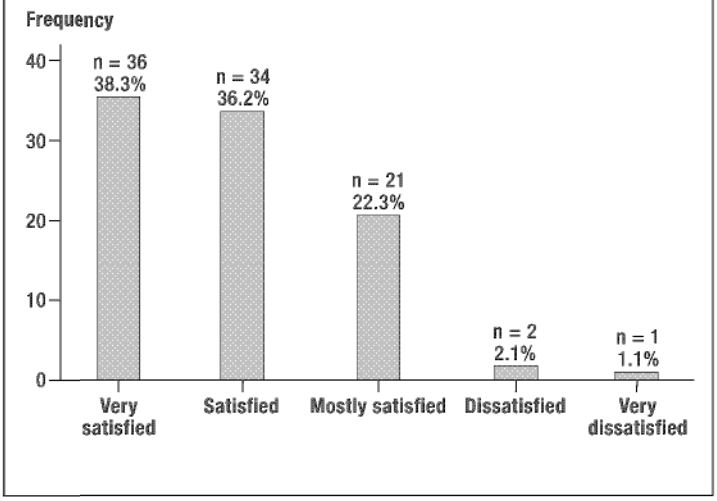
According to Senf, no disruption to an individual's identity is comparable in scale to the development of transsexualism (14). Transsexualism is a dynamic, biopsychosocial process which those affected cannot escape. An affected individual gradually becomes aware that he or she is living in the wrong body. The feeling of belonging to the opposite sex is experienced as an unchangeable, unequivocal identity (14, 15). The individual therefore strives to change his or her inner identity. This change is associated with a change in psychosocial role, and in most cases with hormonal and/or surgical reassignment of the body to the desired gender (14). Coping with the development of transsexualism poses enormous challenges to those affected and often leads to a considerable psychological burden. In some cases this results in mental illness. Transsexualism itself need not lead to a mental disorder (14).

FIGURE 1



How satisfied are you with your outward appearance?
(103 responses)

FIGURE 2



How satisfied are you with the aesthetic outcome of your surgery?
(94 responses)

Psychotherapeutic support is beneficial and is a major part of standard treatment and the examination of transsexual individuals in Germany (15).

Methods

Aim

This study aimed to evaluate the effect of male-to-female gender reassignment surgery on the satisfaction of transgender patients.

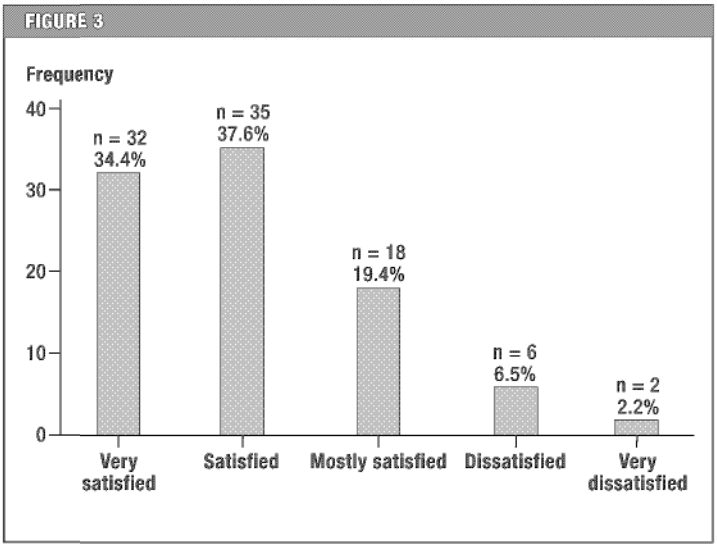
Data collection

Retrospective inquiry involved consecutive inclusion of 254 patients who had undergone male-to-female gender reassignment surgery involving penile inversion vaginoplasty at Essen University Hospital's Department of Urology between 2004 and 2010. All patients received a questionnaire *(eBox 2)* by post, with a franked return envelope. The questions were contained within a follow-up questionnaire developed by Essen University Hospital's Department of Urology (16). Because the process was anonymized, patients who had not sent back the questionnaire could not be contacted. The diagnosis of "transidentity" had been made previously following specialized medical examination and in accordance with ICD-10.

Statistics

Statistical evaluation was performed using SPSS (Statistical Package for the Social Sciences, 17.0). Correlation analyses were performed using SAS (Statistical Analysis System, 9.1 for Windows). The distribution of categorical and ordinal data was described using absolute and relative frequencies. Fisher's exact test was used to compare categorical and ordinal variables in independent samples. The Mann–Whitney U-test was used to compare satisfaction scale distribution of two independent samples. This nonparametric test was used in preference to the *t*-test because the Shapiro–Wilk test indicated that distribution was not normal. Spearman's correlation analysis was performed.

FIGURE 3



How satisfied are you with the functional outcome of your surgery?
(93 responses)

Results

A total of 119 completed questionnaires were returned, all of which were included in the evaluation. This represents a response rate of 46.9%. Because the questionnaires were anonymous, no data on patients' ages could be obtained. The average age of a comparable cohort of patients at Essen University Hospital's

TABLE 2

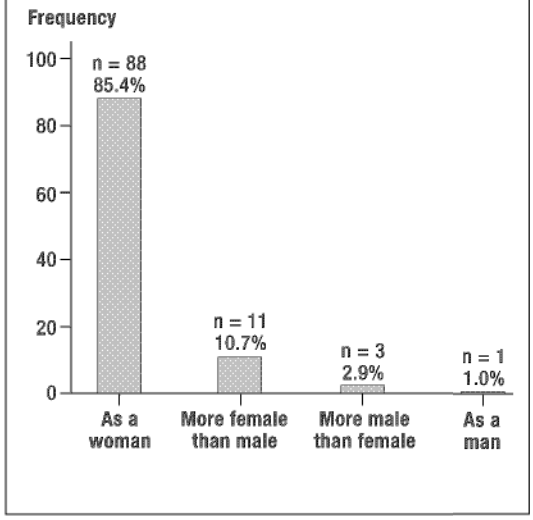
Overview of subjective satisfaction (by number of study participants)

Author	Year	No. (MTF/FTM)	Country	Satisfaction (%)			Response rate (%)
				Functional[*1]	Aesthetic[*2]	Overall	
Imbimbo et al. (20)	2009	139 (139/0)	Italy	56	78	94	–
Hess et al.	2014	119 (119/119)	Germany	91	97	96	47
Perovic et al. (e4)	2000	89 (89/0)	Serbia	87	87	–	–
Happich et al. (21)	2006	56 (33/23)	Germany	–	82	>90	48
Löwenberg et al. (19)	2010	52 (52/0)	Germany	84	94	69	49
Salvador et al. (e5)	2012	52 (52/0)	Brazil	88	–	100	75
Johansson et al. (e6)	2010	42 (25/17)	Sweden	–	–	95	70
Hepp et al. (22)	2002	33 (22/11)	Switzerland	80	75	–	70
de Cuypere et al. (2)	2005	32 (32/0)	Belgium	79	86	–	–
Krege et al. (16)	2001	31 (31/0)	Germany	76	94	–	67
Amend et al. (e7)	2013	24 (24/0)	Germany	100	100	–	–
Blanchard et al. (e8)	1987	22 (22/0)	Canada	73	90	–	–
Giraldo et al. (e9)	2004	16 (16/0)	Spain	100	100	–	–

[*1]Functional satisfaction includes satisfaction with depth and breadth of the neovagina and satisfaction with penetration or intercourse
[*2]Aesthetic satisfaction includes satisfaction with appearance of external genitalia
MTF: male-to-female; FTM: female-to-male

How do you see yourself today?
(103 responses)

FIGURE 4



Department of Urology between 1995 and 2008 (17) was 36.7 years (16 to 68 years). The median time since surgery was 5.05 years (standard deviation: 1.6 years; range: 1 to 7 years). Not all patients had completed the questionnaire in full, so for some questions the total number of responses is not 119.

Following surgery, 63 of 103 patients (61.2%) were satisfied with their outward appearance as women, and a further 27 (26.2%) were very satisfied *(Figure 1)*. 45.5% (n = 50) were very satisfied with the gender reassignment surgery process, 30% (n = 33) satisfied, 22.7% (n = 25) mostly satisfied, and 1.8% (n = 2) dissatisfied. *Figure 2* shows the high rates of subjective satisfaction with the aesthetic outcome of surgery. Overall, approximately three-quarters (70 of 94 responses) reported that they were satisfied or very satisfied. A further 21 (22.3%) were mostly satisfied. Figures for satisfaction with the functional outcome of surgery were similar *(Figure 3)*. A total of 67 of 93 respondents (72%) were satisfied or very satisfied. A further 18 patients (19.4%) were mostly satisfied. *Table 2* compares the rates of subjective satisfaction with aesthetic and functional outcome with other studies.

In order to gather information on patients' general satisfaction with their lives, they were asked to place themselves on a Likert scale ranging from 1 ("very dissatisfied") to 10 ("very satisfied"). Of the total of 102 respondents, 7 (6.9 percent) selected scores from 1 to 3 (2 × 1, 1 × 2, 4 × 3) and 39 (38.2%) scores from 4 to 7 (4 × 4, 16 × 5, 8 × 6, 11 × 7). 56 patients (54.9%) placed themselves in the top third (32 × 8, 13 × 9, 11 × 10). 88 of 103 participants (85.4%) felt completely female following surgery, and 11 (10.7%) mostly female *(Figure 4)*. 69 of 102 women (67.6%) saw themselves as fully accepted as women by society, 25 (24.5%) mostly, and 6 (5.9%) rarely. Two women (2.0%) were not sure of their answer to this question. Of 95 respondents, 65 (68.4%) answered with a clear "Yes" that their life had become easier since surgery. 14 (14.7%) found life somewhat easier, 9 (9.5%) somewhat harder, and 7 (7.4%) harder. Expectations of life as a woman

were completely fulfilled for 51 of 102 (50.0%) women, and mostly for 41 (40.2%). The expectations of 6 (5.9%) patients were mostly not fulfilled, and those of 4 (3.9%) were not fulfilled at all.

There was a correlation between self-perception as a woman ("How do you see yourself today?") and perceived acceptance by society ($r = 0.495$; $p < 0.01$). There was also a correlation between self-perception and answers to whether life had become easier since surgery ($r = 0.375$; $p < 0.01$) and whether expectations of life as a woman had been fulfilled ($r = 0.419$; $p < 0.01$). Patients who saw themselves completely as women reported higher scores for current satisfaction with their lives than patients who only saw themselves as more female than male ($r = 0.347$; $p < 0.01$).

Patients were asked how easy they found it to achieve orgasm. A total of 91 participants answered this question: 75 (82.4%) reported that they could achieve orgasm. Of these, 19 (20.9%) still achieved orgasm very easily, 39 (42.9%) usually easily, and 17 (18.7%) rarely easily. Participants were also asked to compare their experience of orgasm before and after surgery (more intense/the same/less intense). Over half of those who answered this question (43 of 77, 55.8%) experienced more intense orgasm postoperatively, and 16 patients (20.8%) experienced the same intensity.

TABLE 3

Ability to achieve orgasm following male-to-female gender reassignment surgery (by number of study participants)

Author	Year	No. of patients (n)	Able to achieve orgasm (%)
Lawrence (e10)	2005	232	85
Lawrence (e11)	2006	226	78
Hess et al.	2014	119	82
Perovic et al. (e4)	2000	89	82
Goddard et al. (30)	2007	64	48
Hage and Karim (e12)	1996	59	80
Salvador et al. (e5)	2012	52	88
Eicher et al. (e13)	1991	50	82
Bentler (e14)	1976	42	67
Jarrar et al. (e15)	1996	37	60
de Cuypere et al. (2)	2005	32	50
Krege et al. (16)	2001	31	87
Selvaggi et al. (e16)	2007	30	85
Rehman et al. (24)	1999	28	79
Amend et al. (e7)	2013	24	96
van Noort and Nicolai (e17)	1993	22	82
Blanchard et al. (e8)	1987	22	82
Eldh (e18)	1993	20	100
Schroder and Carroll (e19)	1999	17	66
Rakic et al. (e20)	1996	16	63
Ross and Need (e21)	1989	14	85
Lief and Hubschman (e22)	1993	14	29
Giraldo et al. (e9)	2004	16	100
Lindemalm et al. (e23)	1986	13	46
Rubin (e24)	1993	13	92
Stein et al. (e25)	1990	10	80
Freandt et al. (e26)	1993	10	70

Discussion

According to Sohn et al. (18), subjective satisfaction rates of 80% can be expected following gender reassignment surgery. Löwenberg (19) reported 92% general satisfaction with the outcome of gender reassignment surgery. The study by Imbimbo et al. (20) found a similarly high satisfaction rate (94%); however, subjective assessment of general satisfaction and the question of whether or not patients regretted the decision to undergo gender reassignment surgery were queried in one combined question. It is likely that most patients do not actually regret their decision to undergo surgery, even though general postoperative satisfaction is limited. Löwenberg's figures also show this (19): 69% of those asked were satisfied with their overall life situation, but 96% would opt for surgery again. In the authors' own study population, general satisfaction with surgery was achieved in 87.4% of patients. Regardless of surgical results, over half of patients (54.9%) were in the top third ("completely satisfied") and a further 38.2% in the middle third ("fairly satisfied") of the general life satisfaction scale.

A retrospective survey performed by Happich (21) found more than 90% satisfaction with gender reassignment. Sexual experience following surgery is a very important factor in satisfaction with gender reassignment. It depends essentially on the functionality of the neovagina. Figures for satisfaction with functional outcome range from 56% to 84% (16, 19, 20, 22, 23). In the authors' population, satisfaction with function was 72% ("very satisfied" and "satisfied") or 91.4% (including also "mostly satisfied"). According to Happich (21), satisfaction with sexual experience is positively correlated with satisfaction with outcome of surgery. Other studies (16, 23–25) have also found surgical outcome to be one of the essential factors in postoperative satisfaction. Löwenberg (19) also found a correlation between satisfaction with surgery and satisfaction with aesthetic appearance of the external genitalia. In our study, almost all patients (98.2%) were satisfied with the gender reassignment surgery process ($n = 50$, 45.5% "very satisfied"; $n = 33$, 30% "satisfied"; $n = 25$, 22.7% "mostly satisfied").

The Imbimbo et al. working group (20) reported 78% satisfaction with aesthetic appearance of the neogenitalia (36% "very satisfied," 32% "satisfied," 10% "mostly satisfied"). Happich found 82.1% satisfaction with outcome of surgery (46 of 56 patients). Of these, 33.9% of patients reported high satisfaction and 48.2%

good to medium satisfaction (21). A similar value was obtained in the survey by Hepp et al. (22). Löwenberg (19) found higher values (94%) for satisfaction with aesthetic outcome of surgery. This population included 106 male-to-female transgender individuals who underwent surgery at Essen University Hospital's Department of Urology between 1997 and 2003. In the population described here (254 patients, 2004 to 2010) satisfaction with aesthetic outcome was still higher (96.8%).

Orgasm was possible for 82.4% of study participants. The ability to achieve orgasm was lower than in an earlier study population (16). Figures in the literature vary widely (29% to 100%) and sometimes include small case numbers *(Table 3)*. Overall, the figures for this study match those of comparable studies of a similar size. Finally, it is not clear why more than half the participants experienced orgasm more intensely following surgery than preoperatively. One possible explanation is that postoperatively patients were able to experience orgasm in a body that matched their perception.

Limitations

The response rate of less than 50% must be mentioned as a shortcoming of this study. This may have led to a bias in the results. If all patients who did not take part in the survey were dissatisfied, up to 50.1% and 54.6% would be dissatisfied with aesthetic or functional outcome respectively. According to Eicher, the suicide rate in transgender individuals following successful surgery is no higher than in the general population (26), so suicide is a very unlikely reason for nonparticipation. Contacting transfemale patients for long-term follow-up after successful surgery is generally difficult (2, 3, 22, 23, 25, 27, 28). This may be because a patient has moved since successful surgery, for example, (21). Postoperative contact is particularly difficult in countries such as Germany which have no central registers. Response rates to surveys in retrospective research are between 19% (28) and 79% (29). Goddard et al. obtained a response rate of 30% in a retrospective survey following gender reassignment surgery (30). A follow-up survey performed by Löwenberg et al. had a similar response rate, 49% (19). It is also possible that the positive results of our survey represent patients' wish for social desirability rather than the real situation. However, this cannot be verified retrospectively.

Conclusion

Taking into account the limitations mentioned above, the high rates of subjective satisfaction with outward female appearance and with aesthetic and functional outcome of surgery indicate that the study participants benefited from gender reassignment surgery.

KEY MESSAGES

- At the core of the transsexual experience lies the awareness that one is a member of a realistically perceived anatomical sex (matching of genotype and phenotype), but a subjective feeling of belonging to the other gender.
- Change to the gender inwardly identified with is associated with a change in psychosocial role and in most cases with hormonal and surgical reassignment of the body to the desired gender.
- Although transsexualism itself is not a mental disorder, it can favor the development of mental problems.
- Transsexualism is a dynamic, biopsychosocial process which affected individuals cannot escape.
- The high rates of subjective satisfaction with outward female appearance and with aesthetic and functional outcome of surgery indicate that study participants benefited from gender reassignment surgery.

Conflict of interest statement

Dr. Hess has received reimbursement of conference fees and travel expenses from AMS American Medical Systems.

The other authors declare that no conflict of interest exists.

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REFERENCES

1. Coleman E, Bockting W, Botzer M, et al.: Standards of care for the health of transsexual, transgender, and gender-nonconforming people, Version 7. Int J Transgend 2012; 13: 67.
2. de Cuypere G, T'Sjoen G, Beerten R, et al.: Sexual and physical health after sex reassignment surgery. Arch Sex Behav 2005, 34: 679–90.
3. Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, Landén M: Long-term follow-up of transsexual persons undergoing sex reassignment surgery: Cohort Study in Sweden. PLoS One 2011; 6: 8.
4. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A: Psychiatric comorbidity in gender identity disorder. J Psychosom Res 2005; 58: 259–61.
5. Hage JJ, Karim RB: Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. Plast Reconstr Surg 2000; 105: 1222–27.
6. Klein C, Gorzalka BB: Sexual functioning in transsexuals following hormone therapy and genital surgery: a review. J Sex Med 2009; 6: 2922–39.
7. Gijs L, Brewaeys A: Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. Annu Rev Sex Res 2007; 18:1.
8. Weitze C, Osburg S: Transsexualism in Germany: empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. Arch Sex Behav 1996; 25: 409–25.
9. de Cuypere G, van Hemelrijck M, Michel A, et al.: Prevalence and demography of transsexualism in Belgium. Eur Psychiatry 2007; 22: 137–41.
10. Biosnich JR, Brown GR, Shipherd JC, Kauth M, Piegari RI, Bossart RM: Prevalence of gender identity disorder and suicide risk among transgender veterans utilizing veterans health administration care. Am J Public Health 2013; 103: 6.
11. van Kesteren PJ, Gooren LJ, Megens JA: An epidemiological and demographic study of transsexuals in the Netherlands. Arch Sex Behav 1996; 25: 589–600.

12. Garrels L, Kockott G, Michael N, et al.: Sex ratio of transsexuals in Germany: The development over three decades. Acta Psychiatr Scand 2000; 102: 445–8.
13. Pichlo HG: Leistungsrechtliche und sozialmedizinische Kriterien für somatische Behandlungsmaßnahmen bei Transsexualismus: Neue MDK-Begutachtungsanleitung. Blickpunkt der Mann 2010; 8: 8.
14. Senf W: Transsexualität. Psychotherapeut 2008; 53: 12.
15. Becker S, Bosinski HAG, Clement U, et al.: Behandlung und Begutachtung von Transsexuellen Standards der Deutschen Gesellschaft für Sexualforschung, der Akademie für Sexualmedizin und der Gesellschaft für Sexualwissenschaft. Psychotherapeut 1997; 42: 7.
16. Krege S, Bex A, Lummen G, Rubben H: Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. BJU Int 2001; 88: 396–402.
17. Rossi Neto R, Hintz F, Krege S, Rübben H, vom Dorp F: Gender reassignment surgery—a 13 year review of surgical outcomes. Int Braz J Urol 2012; 38: 10.
18. Sohn MH, Hatzinger M, Wirsam K: Operative Genitalangleichung bei Mann-zu-Frau-Transsexualität: Gibt es Leitlinien oder Standards? [Genital reassignment surgery in male-to-female transsexuals: do we have guidelines or standards?]. Handchir Mikrochir Plast Chir 2013; 45: 207–10.
19. Löwenberg H, Lax H, Neto RR, Krege S: Complications, subjective satisfaction and sexual experience by gender reassignment surgery in male-to-female transsexual. Z Sexualforsch 2010; 23: 328–47.
20. Imbimbo C, Verze P, Palmieri A, et al.: A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. J Sex Med 2009; 6: 2736–45.
21. Happich FJ: Postoperative Ergebnisse bei Transsexualität unter besonderer Berücksichtigung der Zufriedenheit – eine Nachuntersuchung. Dissertation Universität Essen-Duisburg 2006.
22. Hepp U, Klaghofer R, Burkhard-Kubler R, Buddeberg C: Behandlungsverläufe transsexueller Patienten: Eine katamnestische Untersuchung. [Treatment follow-up of transsexual patients. A catamnestic study]. Nervenarzt 2002; 73: 283–8.
23. Eldh J, Berg A, Gustafsson M: Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg Suppl 1997; 31: 39–45.
24. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A: The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. Arch Sex Behav 1999; 28: 71–89.
25. Lawrence AA: Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 2003; 32: 299–315.
26. Eicher W: Transsexualismus: Möglichkeiten und Grenzen der Geschlechtsumwandlung: Stuttgart: Gustav Fischer Verlag 1992.
27. Lobato MI, Koff WJ, Manenti C, et al.: Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. Arch Sex Behav 2006; 35: 711–5.
28. Rauchfleisch U, Barth D, Battegay R: Resultate einer Langzeitkatamnese von Transsexuellen. [Results of long-term follow-up of transsexual patients]. Nervenarzt 1998; 69: 799–805.
29. Sorensen T: A follow-up study of operated transsexual males. Acta Psychiatr Scand 1981; 63: 486–503.
30. Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR: Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. BJU Int 2007; 100: 607–13.
31. Pauly IB: The current status of the change of sex operation. J Nerv Ment Dis 1968; 147: 460–71.
32. Walinder J: Transsexualism: definition, prevalence and sex distribution. Acta Psychiatr Scand Suppl 1968; 203: 255–8.
33. Hoenig J, Kenna JC: The prevalence of transsexualism in England and Wales. Br J Psychiatry 1974; 124: 181–90.
34. Ross MW, Walinder J, Lundstrom B, Thuwe I: Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. Acta Psychiatr Scand 1981; 63: 75–82.
35. O'Gorman EC: A retrospective study of epidemiological and clinical aspects of 28 transsexual patients. Arch Sex Behav 1982; 11: 231–6.
36. Tsoi WF: The prevalence of transsexualism in Singapore. Acta Psychiatr Scand 1988; 78: 501–4.
37. Eklund PL, Gooren LJ, Bezemer PD: Prevalence of transsexualism in The Netherlands. Br J Psychiatry 1988; 152: 638–40.
38. Landén M, Walinder J, Lundstrom B: Prevalence, incidence and sex ratio of transsexualism. Acta Psychiatr Scand 1996; 93: 221–3.
39. Wilson P, Sharp C, Carr S: The prevalence of gender dysphoria in Scotland: a primary care study. Br J Gen Pract 1999; 49: 991–2.
40. Haraldsen IR, Dahl AA: Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand 2000; 102: 276–81.

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ORIGINAL ARTICLE

Satisfaction With Male-to-Female Gender Reassignment Surgery

Results of a Retrospective Analysis

Jochen Hess, Roberto Rossi Neto, Leo Panic, Herbert Rübben, Wolfgang Senf

eREFERENCES

e1. Olsson SE, Moller AR: On the incidence and sex ratio of transsexualism in Sweden, 1972–2002. Arch Sex Behav 2003; 32: 381–6.

e2. Gomez-Gil E, Trilla Garcia A, Godas Sieso T, et al.: [Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand]. Actas Esp Psiquiatr 2006; 34: 295–302.

e3. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L: Transsexualism in Serbia: a twenty-year follow-up study. J Sex Med 2009; 6: 1018–23.

e4. Perovic SV, Stanojevic DS, Djordjevic ML: Vaginoplasty in male transsexuals using penile skin and a urethral flap. BJU Int 2000; 86: 843–50.

e5. Salvador J, Massuda R, Andreazza T, et al.: Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. Psychiatry Clin Neurosci 2012; 66: 2.

e6. Johansson A, Sundbom E, Hojerback T, Bodlund O: A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 2010; 39: 1429–37.

e7. Amend B, Seibold J, Toomey P, Stenzl A, Sievert KD: Surgical reconstruction for male-to-female sex reassignment. Eur Urol 2013; 64: 141–9.

e8. Blanchard R, Legault S, Lindsay WR: Vaginoplasty outcome in male-to-female transsexuals. J Sex Marital Ther 1987; 13: 265–75.

e9. Giraldo F, Esteva I, Bergero T, et al.: Corona glans clitoroplasty and urethropreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. Plast Reconstr Surg 2004; 114: 1543–50.

e10. Lawrence AA: Sexuality before and after male-to-female sex reassignment surgery. Arch Sex Behav 2005; 34: 20.

e11. Lawrence AA: Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav 2006; 35: 717–27.

e12. Hage JJ, Karim RB: Sensate pedicled neoclitoroplasty for male transsexuals: Amsterdam experience in the first 60 patients. Ann Plast Surg 1996; 36: 621–4.

e13. Eicher W, Schmitt B, Bergner CM: Darstellung der Methode und Nachuntersuchung von 50 Operierten. Z Sexualforsch 1991; 4: 14.

e14. Bentler PM: A typology of transsexualism: gender identity theory and data. Arch Sex Behav 1976; 5: 567–84.

e15. Jarrar K, Wolff E, Weidner W: Langzeitergebnisse nach Geschlechtsangleichung bei männlichen Transsexuellen. Urologe A 1996; 35: 7.

e16. Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P: Genital sensitivity after sex reassignment surgery in transsexual patients. Ann Plast Surg 2007; 58: 427–33.

e17. van Noort DE, Nicolai JP: Comparison of two methods of vagina construction in transsexuals. Plast Reconstr Surg 1993; 91: 1308–15.

e18. Eldh J: Construction of a neovagina with preservation of the glans penis as a clitoris in male transsexuals. Plast Reconstr Surg 1993; 91: 895–900; discussion 901–893.

e19. Schroder M, Carroll RA: New women: Sexological outcomes of male-to-female gender reassignment surgery. J Sex Educ Ther 1999; 24.

e20. Rakic Z, Starcevic V, Maric J, Kelin K: The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav 1996; 25: 515–25.

e21. Ross M, Need J: Effects of adequacy of gender reassignment surgery on psychological adjustment: A follow-up of fourteen male-to-female patients. Arch Sex Behav 1989; 18: 8.

e22. Lief HI, Hubschman L: Orgasm in the postoperative transsexual. Arch Sex Behav 1993; 22: 145–55.

e23. Lindemalm G, Korlin D, Uddenberg N: Long-term follow-up of "sex change" in 13 male-to-female transsexuals. Arch Sex Behav 1986; 15: 187–210.

e24. Rubin SO: Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. Scand J Urol Nephrol Suppl 1993; 154: 1–28.

e25. Stein M, Tiefer L, Melman A: Followup observations of operated male-to-female transsexuals. J Urol 1990; 143: 1188–92.

e26. Freundt I, Toolenaar TA, Huikeshoven FJ, Jeekel H, Drogendijk AC: Long-term psychosexual and psychosocial performance of patients with a sigmoid neovagina. Am J Obstet Gynecol 1993; 169: 1210–4.

e27. Baranyi A, Piber D, Rothenhausler HB: Mann-zu-Frau-Transsexualismus. Ergebnisse geschlechtsangleichender Operationen in einer biopsychosozialen Perspektive. [Male-to-female transsexualism. Sex reassignment surgery from a biopsychosocial perspective]. Wien Med Wochenschr 2009; 159: 548–57.

eBOX 1

Surgical procedure for penile inversion vaginoplasty

1. Open the scrotum.
2. Remove both testicles, including the spermatic cord, from the superficial inguinal ring.
3. Make a circular cut around the skin of the shaft of the penis under the glans and prepare the skin of the shaft of the penis as far as the base of the penis.
4. Separate the urethra from the erectile tissue.
5. Separate the neurovascular bundle from the erectile tissue.
6. Perform bilateral resection of the erectile tissue.
7. Create a space for the neovagina between the rectum and urethra or prostate (the prostate is left intact).
8. Invert the skin of the shaft of the penis and close the distal end.
9. Insert a placeholder into the neovagina (= the inverted skin of the shaft of the penis).
10. Create passages for the neoclitoris (former glans penis) and urethra and then fix in place.
11. Inject fibrin glue into the neovagina.
12. Position the neovagina, including the placeholder.
13. Adjust the labia majora.
14. During a second operation six to eight weeks after the first, the vaginal entrance is constructed and minor plastic corrections are made if necessary.

Surgery lasts an average of approximately 3.5 hours. Preservation of the neurovascular bundle results in a sensitive clitoroplasty. The most common complications in short-term postoperative recovery include superficial wound healing problems around the external sutures. In the medium and long term there is a risk of loss of depth (23, 24, 30, e15, e23, e25) or breadth (24, 30, e11, e19, e25) of the neovagina in particular. These problems usually result from inconsistent dilatation (e27).

eBOX 2

Questionnaire

1. How satisfied are you with your outward appearance?
A) Very satisfied
B) Satisfied
C) Dissatisfied
D) Very dissatisfied

2. How satisfied were you with the gender reassignment surgery process?
A) Very satisfied
B) Satisfied
C) Mostly satisfied
D) Dissatisfied
E) Very dissatisfied

3. How satisfied are you with the aesthetic outcome of your surgery?
A) Very satisfied
B) Satisfied
C) Mostly satisfied
D) Dissatisfied
E) Very dissatisfied

4. How satisfied are you with the functional outcome of your surgery?
A) Very satisfied
B) Satisfied
C) Mostly satisfied
D) Dissatisfied
E) Very dissatisfied

5. How satisfied are you with your life now, on a scale from 1 (very dissatisfied) to 10 (very satisfied)?

6. How do you see yourself today?
A) As a woman
B) More female than male
C) More male than female
D) As a man

7. Do you feel accepted as a woman by society?
A) Yes, completely
B) Mostly
C) Rarely
D) No/Not sure

8. Has your life become easier since surgery?
A) Yes
B) Somewhat easier
C) Somewhat harder
D) No

9. Have your expectations of life as a woman been fulfilled?
A) Yes, completely
B) Mostly
C) Mostly not
D) Not at all

10. How easy is it for you to achieve orgasm?
A) Very easy
B) Usually easy
D) Rarely easy
C) Never achieve orgasm

11. If you compare your orgasm earlier as a man and now as a woman, what is your orgasm like now?
A) More intense
B) Equally/Roughly equally intense
C) Less intense

Effects of Different Steps in Gender Reassignment Therapy on Psychopathology: A Prospective Study of Persons with a Gender Identity Disorder

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ABSTRACT

Introduction. At the start of gender reassignment therapy, persons with a gender identity disorder (GID) may deal with various forms of psychopathology. Until now, a limited number of publications focus on the effect of the different phases of treatment on this comorbidity and other psychosocial factors.

Aims. The aim of this study was to investigate how gender reassignment therapy affects psychopathology and other psychosocial factors.

Methods. This is a prospective study that assessed 57 individuals with GID by using the Symptom Checklist-90 (SCL-90) at three different points of time: at presentation, after the start of hormonal treatment, and after sex reassignment surgery (SRS). Questionnaires on psychosocial variables were used to evaluate the evolution between the presentation and the postoperative period. The data were statistically analyzed by using SPSS 19.0, with significance levels set at $P < 0.05$.

Main Outcome Measures. The psychopathological parameters include overall psychoneurotic distress, anxiety, agoraphobia, depression, somatization, paranoid ideation/psychoticism, interpersonal sensitivity, hostility, and sleeping problems. The psychosocial parameters consist of relationship, living situation, employment, sexual contacts, social contacts, substance abuse, and suicide attempt.

Results. A difference in SCL-90 overall psychoneurotic distress was observed at the different points of assessments ($P = 0.003$), with the most prominent decrease occurring after the initiation of hormone therapy ($P < 0.001$). Significant decreases were found in the subscales such as anxiety, depression, interpersonal sensitivity, and hostility. Furthermore, the SCL-90 scores resembled those of a general population after hormone therapy was initiated. Analysis of the psychosocial variables showed no significant differences between pre- and postoperative assessments.

Conclusions. A marked reduction in psychopathology occurs during the process of sex reassignment therapy, especially after the initiation of hormone therapy. **Heylens G, Verroken C, De Cock S, T'Sjoen G, and De Cuypere G. Reassignment therapy on psychopathology: A prospective study of persons with a gender identity disorder. J Sex Med 2014;11:119–126.**

Key Words. Gender Reassignment Therapy; Psychopathology; Gender Identity Disorder; Gender Dysphoria

Introduction

According to the DSM-IV-R classification, transsexualism or gender identity disorder (GID) is an extreme form of gender dysphoria characterized by a strong and persistent identification with the opposite sex. It is accompanied by the wish to get rid of one's own primary and secondary sex characteristics and to live completely as someone from the opposite sex [1]. In Belgium, the prevalence is around 7.75 male-to-female (MtF) and 2.96 female-to-male (FtM) per 100,000, which is similar to other Western European countries [2].

The etiology of transsexualism remains unclear. Besides biological factors, such as hormonal

abnormalities, morphology of sexual dimorphic brain nuclei, and genetic elements [3–8], psychological and sociocultural factors also seem to be important [3,4].

As far as the therapy for GID is concerned, most countries adopt the standards of care from the World Professional Association for Transgender Health. These standards comprise a variety of therapeutic options, including changes in gender expression and role, hormone therapy, surgery, and psychotherapy. The number and type of interventions applied, and the order in which these take place, may differ from person to person [9]. Most of the persons with GID who attend our clinic wish full sex reassignment including genital surgery, and start with hormonal treatment.

Previous research on the relationship between GID and psychiatric comorbidity has led to divergent conclusions. Some studies suggest that GID is frequently associated with severe psychiatric comorbidity, both on axis 1 and 2, from psychoses and major affective disorders [10,11] to severe personality disorders [12,13]. Others show little or no raised levels of psychopathology in transsexual populations [14–16]. A moderate view is that persons with GID may show more psychopathology, yet no severe neurotic or psychotic disorders [17,18]. Of the various symptoms, depression, anxiety disorders, and adjustment disorders are the most common, followed by substance abuse, suicide, and automutilation [1,17–19]. Due to the incongruence between biological sex and gender identity, many persons with GID also have a disturbed body image, which makes them frequently insecure [20]. These findings imply the existence of a link between gender dysphoria and psychiatric disorders, but do not reveal any information about causality.

In the past decades, various studies have been performed to investigate the effects of sex reassignment therapy on psychological status and psychosocial aspects. In the early years, the number of patients was often small and most of the studies did not employ standardized outcome instruments. In 1990, Green and Fleming reviewed the preceding literature and found out that sex reassignment was effective in reducing gender dysphoria and general well-being [21]. In particular, they emphasized the importance of standardized selection criteria for surgery and the use of standardized instruments for outcome measurement. Green and Fleming's conclusions were reaffirmed by Pfafflin and Junge in their review of approximately 70 outcome studies published between 1961 and 1991 [22].

More recently, Smith et al. prospectively studied the outcomes of sex reassignment and concluded that treatment had a positive effect on gender dysphoria, psychological and social well-being, and sexual satisfaction [23]. Similar results were found in the follow-up study by De Cuypere et al., who especially focused not only on sexuality but also on general health and satisfaction with surgical results [24]. Gomez-Gil et al. [25] showed that persons with GID under hormone therapy scored significantly lower on several Minnesota Multiphasic Personality Inventory scales than patients who had not started hormone treatment yet. Contrary to these results, Haraldsen and Dahl, however, could not find any significant difference when comparing Symptom Checklist-90 (SCL-90) scores in pre- and postoperative patients [26]. Murad et al. [27] and Gys and Brewaeys [28] offered, respectively, comprehensive reviews of studies between 1966 and 2008 and after 1990, and emphasized again the lack of standardization. The American Psychiatric Association Task Force on treatment of GID uses their evidence coding system to evaluate studies concerned with treatment issues: most evidence is on at or below level C (cohort or longitudinal study) (refer to Byne et al. for further reading) [29]. The only controlled study on the effectiveness of sex reassignment surgery (SRS) was conducted by Mate-Kole et al. who compared a waiting list condition with a treatment condition and found better results in the postoperative groups, with the group reporting more social and sexual activity, better employment rates, and lower levels of psychoneurotic pathology indicated by Crown-Crisp Experiential Index scores [30]. Another study from Mate-Kole et al. compared GID patient groups before treatment, during hormone therapy and after SRS and showed that a bigger improvement occurs after SRS than after changing the gender role [31]. This suggests that the effect of sex reassignment on psychological status varies in different phases of the process.

The gender identity clinic of the Ghent University Hospital, Belgium, has evaluated and treated persons with GID since 1985. In the past decade, the number of applicants seeking treatment has increased from 35 to 85 per year in 2012. Eighty-five percent of the applicants come from Flanders, the Dutch speaking part of Belgium. The remaining 15% lives in the French-speaking part. Our clinic has an unique position in Belgium as it offers the full range of diagnostic evaluation and psychotherapeutic support, hormonal

treatment, and surgical interventions. Most of the persons attending our clinic are self-referred or referred by an professional caregiver, about two-thirds presents as a member of identified gender and is, at least partially, in their social transition phase. They are often well informed about treatment modalities, and the majority asks for hormonal and surgical treatment. Costs of psychiatric consultations, hormonal therapy, genital surgery, and breast augmentation and removal are reimbursed. Costs of facial hair removal, female feminization surgery, and speech therapy are not covered.

Aims

Due to a significant improvement of the methodological quality of research on the outcome of sex reassignment, the question no longer centers on whether it helps, but on which part of the treatment is responsible for the biggest improvement in terms of quality of life and reducing psychosocial problems. This study aims to shed light on the differentiating effects of gender reassignment treatment by measuring, in a prospective way, the evolution in psychopathological status during different phases of sex reassignment. Additionally, postoperative results are compared with those of general population in order to investigate whether psychopathology disappears together with sex reassignment therapy, or remains present, albeit possibly to a lesser extent.

Methods

Population

Between June 2005 and March 2009, 90 patients who applied for sex reassignment therapy at our Gender Clinic were asked to participate in this prospective study. Eight patients refused to participate or attended our clinic only once. Eighty-two agreed to participate in the study and were included after giving their informed consent. Twelve patients that were diagnosed with a gender identity disorder not otherwise specified were excluded. Of the remaining 70, all diagnosed with GID, but 12 patients did not undergo full treatment (hormonal and surgical) for several reasons: some were refused because of extensive comorbidity (two individuals with personality disorder, one with acquired brain injury), while others decided for themselves not to start treatment, or desired hormone therapy alone without feeling the need for genital surgery. One patient committed suicide during follow-up. In the end, 57 patients (46 MtF and 11 FtM) filled out the questionnaires, which is described below. The study was approved by the local ethics committee.

Questionnaires

SCL-90, Dutch Adapted Version

The SCL-90 is a widely used 90-item questionnaire consisting of eight subscales (agoraphobia, anxiety, depression, somatization, paranoid ideation/psychoticism, interpersonal sensitivity, hostility, and sleeping problems) and a global score called psychoneuroticism. Higher scores on the global score indicate a higher level of psychopathology. We used the norm group "general population" to compare with the postoperative results from our study population [32,33].

Psychosocial Questionnaires

To obtain the desired information on several demographic and psychosocial parameters, we developed a short questionnaire on employment, living arrangements, sexual orientation, relationships and sexual contacts, social contacts, substance abuse, and suicide thoughts/attempts. This questionnaire was based on the biographic questionnaire patients filled out at the first treatment attendance. The subjective evolution of mood, happiness, anxiety, self-esteem, and body image was also investigated.

Procedure

The study was conducted in a follow-up design. We used the SCL-90 to evaluate psychopathological evolution, with baseline assessment at the time of presentation. Follow-up assessment consists of two moments of measurement: 3–6 months after the start of hormone treatment and 1–12 months after SRS. Psychosocial questionnaires were sent to all patients, and the results were examined in consideration of the biographic data that were collected at the time of presentation. The mean follow-up between the first and the last assessment was 39 months (standard deviation 12.7). The data collection is summarized in Table 1. As all patients completed the gender reassignment treatment, except for 11 patients who did not yet receive SRS when we ended the data collection, there were no dropouts in the study population. Missing data are due to incomplete questionnaires. The response rates for SCL-90 and psychosocial questionnaires were 82.5% and 73.7%, respectively.

Table 1 Data collection

	SCL-90			Psychosocial data	
	Presentation	Follow-up		Presentation	Follow-up
Study group (n = 57)	56*	After HT 47†	After SRS 42‡	54§	42¶

*No baseline SCL-90 assessment was collected from one patient.
†Ten patients did not complete an SCL-90 after hormone therapy.
‡Eleven patients did not yet receive SRS when the data collection was ended. Four others did not complete an SCL-90 after SRS.
§No baseline psychosocial data were collected from three patients.
¶Psychosocial questionnaires were not sent to 11 patients who did not yet receive surgery. Four others did not complete the psychosocial questionnaire.
SRS = sex reassignment surgery; HT = hormone treatment

Statistics

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used to construct a database and perform statistical analyses. A Friedman test was chosen to globally compare SCL-90 scores in the three assessment points, while Wilcoxon tests were used to further compare SCL-90 scores between two assessment points. McNemar and Fisher's exact tests were adopted for comparison of demographic and psychosocial parameters. The significance level was set at $P < 0.05$.

Results

SCL-90

Mean SCL-90 scores are shown in Table 2. Analyses show that a difference exists between the overall psychoneurotic distress scores at the several assessments ($P = 0.003$). Further analysis shows this is due to a decrease in the scores after hormone therapy ($P < 0.001$). No further decrease is observed after SRS. The effect of complete treatment is not more pronounced than that of hormone therapy alone. With regard to the different subscales, differences are found between the measurement points "baseline" and "after SRS" for anxiety ($P < 0.001$), depression ($P = 0.001$), interpersonal sensitivity ($P = 0.005$), and hostility ($P = 0.008$).

Table 2 shows that, unlike scores at time of presentation, SCL-90 scores after hormonal treatment and after surgery are similar to the mean SCL-90 scores of a general population. At the subscale level, the only exceptions are sleeping problems ($P = 0.033$) and, to an almost significant level, psychoticism ($P = 0.051$): after SRS, both are higher compared with a general population. Somatization, that was lower compared with a general population after hormone therapy, settles down to normative levels after SRS.

Psychosocial Questionnaires

Baseline and follow-up demographic and psychosocial parameters are summarized in Table 3. None of the variables show any significant difference between baseline and follow-up. Nonetheless, some tendencies can be distinguished, such as an increase in social contacts and a decrease in substance abuse leading to potentially the complete disappearance of drug abuse. Living

Table 2 Mean SCL-90-scores of "treated population" vs. "general population"

		Study group					
SCL-90 subscale	General population (SD)	Baseline (SD) n = 56	*P*	After hormone therapy (SD) n = 47	*P*	After SRS (SD) n = 42	*P*
ANG [10–50]	12.8 (4.4)	17.0 (6.4)	<0.001	12.4 (5.1)	0.220	13.5 (4.2)	0.286
AGO [7–35]	7.9 (2.3)	9.5 (4.2)	0.065	8.1 (1.8)	0.402	8.2 (2.0)	0.264
DEP [16–80]	21.6 (7.6)	34.7 (14.3)	<0.001	23.8 (9.0)	0.090	24.4 (9.2)	0.086
SOM [12–60]	16.7 (5.3)	18.6 (6.7)	0.042	15.2 (2.7)	<0.001	17.1 (6.2)	0.453
IN [9–45]	12.6 (4.3)	16.6 (7.0)	<0.001	12.8 (4.4)	0.359	15.1 (6.7)	0.051
SEN [18–90]	24.1 (7.6)	31.8 (11.7)	<0.001	24.6 (7.9)	0.277	25.8 (7.1)	0.097
HOS [6–30]	7.2 (2.1)	8.2 (3.0)	<0.001	7.4 (2.0)	0.181	7.2 (1.8)	0.237
SLA [3–15]	4.5 (2.2)	5.8 (3.2)	<0.001	4.4 (1.7)	0.192	5.2 (3.4)	*0.033*
NEUR [90–450]	**118.3 (32.4)**	**157.7 (49.8)**	**<0.001**	**119.7 (32.1)**	**0.359**	**127.9 (37.2)**	**0.082**

P values show differences between "treated population" and "general population."
AGO = agoraphobia; ANG = anxiety; DEP = depression; HOS = hostility; IN = paranoid ideation/psychoticism; NEUR = overall psychoneurotic distress; SCL-90 = Symptom Checklist-90; SD = standard deviation; SEN = interpersonal sensitivity; SLA = sleeping problems; SOM = somatization

Table 3 Socio-demographic and sexual parameters at time of presentation and at follow-up

	Presentation (n = 54)		Follow-up (n = 42)	
	n	%	n	%
Relationship				
None	32	58.2	22	52.4
Stable	22	44.0	18	42.6
Variable	1	1.8	2	4.8
Living situation				
Alone	18	32.1	18	42.9
With partner	21	37.5	16	38.1
With parents	15	26.8	5	11.9
Other	2	3.6	3	7.1
Employment				
Employed	37	66.1	25	59.5
Unemployed	9	16.1	6	14.3
Other (student, retirement, etc.)	10	17.9	11	26.2
Sexual contacts				
None	21	38.2	20	47.6
Only in a stable relationship	25	45.5	19	45.2
Variable	9	16.4	3	7.1
Social contacts				
Good friends	41	73.2	37	88.1
Superficial acquaintances	8	14.3	3	7.1
None	7	12.5	2	4.8
Drugs				
Alcohol abuse	8	14.8	1	2.4
Cannabis	4	7.4	0	0
Other drugs	2	3.7	0	0
Suicide attempt	5	9.4	4	9.3

situations changed with more people living alone and fewer with their parents. Also, "other" employment went up while employment went down. Reports of no sexual relationship went up, while the prevalence of suicide attempts did not change.

After treatment, the majority of patients indicated that they have a better mood, are happier, and feel less anxious than before (Table 4). They also seem to be more self-confident and encounter a better body-related experience, indicating a less distorted self-image than before treatment.

Most patients (57.9%) subjectively experienced the biggest progress after the start of hormone therapy. 31.6% felt the biggest evolution after SRS and 10.5% already noticed the most important change during the diagnostical phase.

Discussion

Analysis of the SCL-90 scores in the treated group has shown that sex reassignment therapy does influence the level of psychopathology in GID patients, with significant reduction in anxiety, depression, somatization, psychoticism, interpersonal sensitivity, hostility, and overall psychoneurotic distress. Although not strictly comparable, results of lower levels of psychopathology in postoperative transsexuals are consonant with other studies or reviews that use independent pre- and postoperative groups [21–25,27]. The findings that, after SRS, somatization is returning to normal again and psychoticism is almost higher compared with a general population ($P = 0.051$) could be explained by an initial euphoria caused by the relief they experience after starting hormonal treatment. Furthermore, sleeping problems become significantly higher after SRS compared with a general population. After SRS, transpeople probably experience more distress as they are again confronted with stigma and other burdens.

While Mate-Kole et al. suggested the most important factor to be SRS [31], we found that the biggest decrease in psychological dysfunctioning is caused by initiation of hormone therapy or confirmation of the diagnosis by a professional caregiver. This finding was consistent with the subjective feeling of most treated patients and suggests that recognition and acceptation of the GID play an important role in their transition process.

The comparison of pre- and postoperative SCL-90 scores with the mean score of a general population provided further information on the effect of treatment. In agreement with several other studies [10–12,17,18], our GID population scored significantly higher on psychopathology than a general population at the time of presentation, while that difference completely disappeared

Table 4 Subjective psychological evolution since presentation and suicide thoughts at the moment of follow-up

	Study group (n = 42)	
	n	%
Mood		
Better	40	95.2
Similar	2	4.8
Happiness		
Happier	39	92.9
Similar	0	0.0
Less happy	0	0.0
Anxiety		
Less anxious	34	81.0
Similar	6	14.3
More anxious	2	4.8
Self-confidence		
More self-confident	33	78.6
Similar	8	19.0
Less self-confident	1	2.4
Body-related experience		
Better	41	97.6
Similar	1	2.4
Suicide thoughts	7	16.7

after hormonal treatment. This finding implies the existence of a relationship between gender dysphoria and psychiatric comorbidity, and suggests that treatment not only causes a decrease in the gender dysphoria, as documented in other studies [21–23], but also a resolution of concomitant psychopathology.

The distinguished trends in demographic and psychosocial parameters are comparable with some findings in literature [23,24]. The presumption that sex reassignment has a positive influence on employment [30,34] could not be confirmed, probably due to the relatively short follow-up period. The finding that regular employment goes down, and "other" employment goes up, could fit in the daily practice observation that transpeople quit with their former jobs and start studying again. Compared with previous literature results that detected substance abuse in up to 60% of GID patients [11,12], we noticed very little abuse in our population. Possible explanations could be that our population was relatively small and the question rather subjective, and that problematic abuse forms a relative contraindication for sex reassignment therapy. Both suicide attempt percentages (10.9% at time of presentation, 9.8% at follow-up) were also slightly lower than those described in literature [16]. The latter finding is in accordance with some recent studies with regard to the high prevalence of suicidality in transpeople, even after their sex reassignment therapy [35].

The strengths of this study lie in its follow-up design and the size of the population. The study population of 57 participants represents one of the larger studies of its kind. To our knowledge, it is the first publication that focuses on the effects of the separate parts of the sex reassignment therapy. Nevertheless, several limitations can be discussed. We are acutely aware of the presence of selection bias: a significant percentage of gender dysphoric people never attends our or "a" gender clinic and this may be accounted for several reasons, including psychosocial factors. The used questionnaires form another source of bias: SCL-90 results are based on a "snapshot" measurement that may not be representative of one's general mental state. Furthermore, the follow-up period was too short to evaluate the effects of treatment on outcome measures as work and relationships. Finally, we certainly have to allow for the spontaneous evolution of complaints due to environmental factors and the passing of time. On the whole, our study population is a selected group that is not fully representative for the larger group of gender dysphoric people: they all fulfilled criteria for GID and were eligible for SRS. This perspective might certainly have an influence on the level of psychoneurotic distress. If there had been less certainty, at the end of the diagnostic phase and after initiation of hormonal treatment, about receiving SRS, results could have been different.

Future research challenges especially lie in comparing treated persons with GID with untreated patients. Additional questionnaires, including in-depth interviews, should investigate more thoroughly the specific effects of therapy on psychopathology and psychosocial state. Also, further exploration in patients seeking hormonal therapy without expressing desire for SRS is warranted, as we found initiation of hormonal therapy to be a major event in reducing psychopathology.

Conclusion

In conclusion, our findings confirm the hypothesis that sex reassignment therapy had a positive influence on co-occurring psychopathology if present in GID patients at presentation, by lowering the overall level of psychoneurotic distress. After treatment, our GID population showed a similar level of psychopathology compared with a general population, while they scored significantly higher at baseline. The most important effect seemed to result from the confirmation of the diagnosis and the initiation of hormone therapy, a finding that offers insights into a more individualized approach to persons suffering from GID.

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References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition, text rev. Washington DC: American Psychiatric Association; 2000.
2 De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. Eur Psychiatry 2007;22:137–41.
3 Cohen-Kettenis P, Gooren L. Transsexualism: A review of etiology, diagnosis and treatment. J Psychosom Res 1999;46: 315–33.
4 Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. Eur J Endocrinol 2001;145:365–76.
5 Zhou JN, Hofman MA, Gooren LJ, Swaab DF. A sex difference in the human brain and its relation to transsexuality. Nature 1995;378:68–70.
6 Swaab D. Sexual differentiation of the human brain: Relevance for gender identity, transsexualism and sexual orientation. Gynecol Endocrinol 2004;19:301–12.
7 Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile in transsexualism? J Sex Med 2011;8:475–8.
8 Heylens G, De Cuypere G, Zucker KJ, Schelfaut C, Elaut E, Vanden Bossche H, De Baere E, T'Sjoen G. Gender identity disorder in twins: A review of the case report literature. J Sex Med 2012;9:751–7.
9 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of care for the health of transsexual, transgender, and gender nonconforming people, 7th Version. Int J Transgenderism 2011;13:165–232.
10 À Campo J, Nijman H, Merckelbach H, Evers C. Psychiatric comorbidity of gender identity disorders: A survey among Dutch psychiatrists. Am J Psychiatry 2003;160:1332–6.
11 De Cuypere G, Jannes C, Rubens R. Psychosocial functioning of transsexuals in Belgium. Acta Psychiatr Scand 1995;91: 180–4.
12 Bodlund O, Kullgren G, Sundbom E, Höjerback T. Personality traits and disorders among transsexuals. Acta Psychiatr Scand 1993;88:322–7.
13 Madeddu F, Prunas A, Hartmann D. Prevalence of axis II disorders in a sample of clients undertaking psychiatric evaluation for sex reassignment surgery. Psychiatr Q 2009;80: 261–7.
14 Cole CM, O'Boyle M, Emory LE, Meyer WJ. Comorbidity of gender dysphoria and other major psychiatric diagnoses. Arch Sex Behav 1997;26:13–26.
15 Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand 2000;102:276–81.
16 Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. Psychiatry Clin Neurosci 2010;64:514–9.
17 Heylens G, Elaut E, Kreukels BPC, Paap MSC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen IR, De Cuypere G. Psychiatric characteristics in transsexual individuals: A multi-centre study in four European countries. Br J Psychiatry 2013. doi: 10.1192/bjp.bp.112.121954.
18 Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res 2005;58:259–61.
19 Gómez-Gil E, Trilla A, Salaremo M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. Arch Sex Behav 2009;38:378–92.
20 Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology 2008;41:96–100.
21 Green R, Fleming D. Transsexual surgery follow-up: Status in the 1990s. Annu Rev Sex Res 1990;1:163–74.
22 Pfafflin F, Junge A. Sex reassignment: Thirty years of international follow-up studies after SRS. A comprehensive review, 1961–1991. Dusseldorf, Germany: Symposium Publishing.
23 Smith YLS, Van Goozen SHM, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med 2004;35: 89–99.
24 De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Van Steenwegen A, Rubens R. Sexual and physical health after SRS. Arch Sex Behav 2005;34:679–90.
25 Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: Comparison of patients in prehormonal and presurgical phases. J Pers Assess 2008;90:368–74.
26 Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand 2000;102:276–81.
27 Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol 2010;72:214–31.
28 Gys L, Brewaeys A. Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. Annu Rev Sex Res 2007;18:178–224.
29 Byne W, Bradley S, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Pleak RR, Tompkins DA. Report of the APA Task Force on treatment of gender identity disorder. Am J Psychiatry 2012;169:1–35.
30 Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry 1990;157: 261–4.
31 Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry 1988;152:550–3.
32 Arrindell WA, Ettema JHM. Symptom Checklist SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator. Amsterdam: Harcourt Test Publishers; 2005.

33 Derogatis LR, Lipman RS, Covi L. SCL-90: An outpatient psychiatric rating scale—Preliminary report. Psychopharmacol Bull 1973;9:13–28.
34 Vennix P. Genderidentiteit en werk bij man-naar-vrouw transgenders. Tijdschr Seksuol 2002;26:245–52.
35 Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GK, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: Review and recommendations. J Homosex 2011;58:10–51.

Supporting sexuality and improving sexual function in transgender persons

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Abstract | Sexuality is important for most cisgender as well as transgender persons and is an essential aspect of quality of life. For both the patient and their clinicians, managing gender dysphoria includes establishing a comfortable relationship with sexual health issues, which can evolve throughout the course of gender-affirming treatment. Gender-affirming endocrine treatment of transgender men and women has considerable effects on sex drive and sexual function. Gender-affirming surgery (GAS) can improve body satisfaction and ease gender dysphoria, but surgery itself can be associated with sexual sequelae associated with physical constraints of the new genitals or postsurgical pain, psychological difficulties with accepting the new body, or social aspects of having changed gender. In general, a positive body image is associated with better sexual function and satisfaction, but satisfaction with sexual function after GAS can be present despite dissatisfaction with the surgery and vice versa. Factors involved in the integrated experience of gender-affirming treatment and the way in which sexuality is perceived are complex, and supporting sexuality and improving sexual function in transgender patients is, correspondingly, multifaceted. As the transgender patient moves through their life before, during, and after gender-affirming treatment, sexuality and sexual function should be considered and maximized at all stages in order to improve quality of life.

Gender identity refers to an innate and deeply felt identification as a female, male, or some other nonbinary gender, and is one of many aspects of sex or gender[1,2] (BOX 1). For many years, gender identity was viewed as binary: an individual could be either female or male. However, more recently, gender identity has become viewed as a spectrum, whereby female and male are two of many gender identities that can also include nonbinary, gender fluid, transgender, gender queer, transgender masculine, and transgender feminine[3,4]. The gender identity of a person can be congruent or incongruent with the sex assigned at birth. Gender dysphoria refers to discomfort or distress sometimes caused by gender incongruence[5]. Transition is the process by which someone starts to present themselves permanently accordingly to their gender identity[6]. Some individuals ease their dysphoria with a social transition (change of name, gender expression, and/or gender role), whereas others might seek gender-affirming treatment in order to alter the body so that it is in line with their gender identity, alleviating gender dysphoric symptoms[5–8]. The latter is sometimes called medical transition.

The global prevalence of diagnosed gender dysphoria has been estimated in two meta-analyses (including studies up to 2014) at 4.6–6.8 per 100,000 (REFS[9,10]). Since then, a study from the Netherlands estimated the prevalence of individuals who have undergone gender-affirming treatment before 2015 to be 27.7 per 100,000 people (95% CI 26.8–28.6)[11]. In a report that included data up to 2015, self-reported gender dysphoria or self-identified transgender identity had a global prevalence of 871 per 100,000 (95% CI 519–1,224) or 355 per 100,000 (95% CI 144–566) with removal of an outlier[10]. Since then, 500 of 100,000 people (0.5%, 95% CI 0.4–0.7%) from a representative sample of the population aged ≥22 years in Stockholm county, Sweden, answered 'yes' when asked if they would like to change their body with hormones or surgery to be more like a person of a different sex[12].

The incidence and prevalence of gender dysphoria is increasing[9,11,13]. In Sweden the incidence of applications for change of legal gender increased almost threefold from 0.20 per 100,000 per year in 1972–1980 to 0.57 per 100,000 per year in 2001–2010. In the Netherlands a 20-fold increase of assessment from 34 in 1980 to 686 in 2015 was reported[11].The increase might reflect an increase in people openly discussing gender as society has become more inclusive, but a true increase in prevalence cannot be ruled out[9,10,13]. Conceptualization of gender incongruence and gender dysphoria changes continuously, as has the language describing these phenom

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Key points

- Evaluation of sexual dysfunction in transgender persons is multidimensional.
- Hormonal treatment is likely to increase sexual desire in transgender men and decrease desire in transgender women.
- A reduction in sexual drive is not necessarily a concern, but can, in fact, be appreciated or even desirable for some patients.
- Before initiating hormonal or surgical treatment, wishes and hopes about future sexual function should be explored.
- Sexual problems in transgender persons can be trans specific or not. General principles in sexual medicine apply to both cisgender and transgender persons.

The transgender population is heterogeneous[5,15] and many efforts have, therefore, been made to stratify the population into subgroups, in order to predict treatment outcomes and to attempt to understand the aetiology of gender incongruence[16,17]. Besides subgrouping assigned females or males at birth, the most common subdivisions have been based on early-onset and late-onset gender dysphoric symptoms. No strict definitions exist, but early onset is often defined as gender incongruence or gender dysphoric symptoms during childhood or before puberty, or used to describe a patient who fulfils the diagnostic criteria for gender dysphoria during childhood; late onset is often defined as during or after puberty[18]. Subdivisions have also been made based on the person's sexual orientation[18–23]. However, information regarding age of onset or sexual orientation in clinical studies is likely to be biased, as many treatment facilities have restricted access to care for certain subgroups. Thus, in order to be offered treatment, patients might have adjusted or misreported their medical history[15,16,18,24]. In one study, 12% of transgender women claimed that they had concealed their sexual orientation at assessment[25]. Likewise, in a Finnish study, 44% of patients reported that they delivered a falsified story at assessment in order to access gender-affirming treatment[24]. Today, fewer obstacles restrict access to gender-affirming treatment, so information collected should become more reliable[19].

Transgender health care is multidisciplinary, as described in the Standards of Care version 7 (SOC 7) from the World Professional Association for Transgender Health (WPATH)[5]. Not all individuals with gender dysphoria need, or can access, the full spectrum of different gender-affirming treatments, and many countries still do not allow legal sex change including assigned official documents stating a new legal sex or gender marker, for example Brazil, Chile, Cyprus, Macedonia, Tanzania, Thailand, and Uganda. In many countries, a change of legal sex or gender marker is only possible if the applicant has fulfilled certain requirements, such as having a medical diagnosis, living according to the preferred gender role, having undergone any gender-affirming treatment, having undergone gender-affirming genital surgery, or being sterile. Change of legal sex or gender marker based on self-determination via an easy administrative procedure is only possible in a few countries (Argentina, Colombia, Denmark, Ireland, Malta, and Norway)[26]. This Review is based solely on literature published in countries where gender dysphoria is recognized as a medical condition and where access to care is, at least for some patients, affordable. The global situation is completely different: in many countries transgender individuals are not recognized, in some countries they are regarded as criminals, and in some jurisdictions being transgender is even considered a legitimate reason for the death penalty[27,28]. Even in more tolerant parts of the world, transgender persons face social marginalization, stigma, discrimination, violence, and difficulties in accessing health care[2,14,26,29,30]

Box 1 | **Aspects of gender**[291]

Legal gender
The gender defined in legal documents and birth certificate.

Chromosomal sex
Karyotype describing the presence or absence of Y and/or X chromosomes.

Hormonal sex
Female or male sexual hormone pattern.

Anatomical sex
Female or male primary and secondary sex organs.

Gender identity
The perception of being a man, woman, or some other gender.

Gender expression
How the person expresses their gender identity in a social context with more or less well-defined social gender characteristics, for example the way of dressing.

Gender role
Behaviours, attitudes, and personality traits, which in a given society and historical period are typically attributed to, expected from, or preferred by persons of that gender.

Sexual health is defined by WHO as being a state of physical, emotional, mental, and social well-being related to sexuality; it is not merely the absence of disease, dysfunction, or infirmity[31]. Sexual dysfunctions arise when impaired sexual function causes distress and are often divided into four categories: lack of desire or interest, arousal dysfunction, orgasm and/or ejaculatory dysfunctions, and pain during sexual activities[32,33]. Sexual desire is often seen as an amalgamation of different components: sexual drive (biological), sexual motivation (cognitive), and responsiveness to sexual stimuli[34]. Sexuality and sexual function are influenced by biological, intrapersonal, and interpersonal factors, as well as socioeconomic, political, cultural, ethical, legal, historical, religious, and spiritual factors[31].

Sexual satisfaction refers to the affective response to the individuals' expectations or evaluation of the balance of negative and positive dimensions of someone's sexuality and is more than simply sexual function[35,36], which is just one of the determinants of sexual satisfaction and sexual health[35]. Cross-sex hormonal therapy (CHT) and gender-affirming surgery (GAS) can affect sexual functions such as desire and/or sexual interest, arousal, and ability to orgasm[37,38]. However, body image, self-esteem, psychological well-being, and sexual anxiety are also important aspects of sexual health and satisfaction[35,39–41]. Gender-affirming treatments ease gender incongruence and gender dysphoria[42], but body image, body self-esteem, and psychological well-being might be affected even after treatment[40,43,44].

In this Review, we will identify clinical factors of importance for the sexual health of transgender persons before, during, and after undergoing different

Box 2 | **List of definitions**

Androphilic
Sexual orientation towards men or masculinity[81].

Birth-assigned sex
The sex and/or gender that was assigned at birth. This supersedes the terms 'biological sex', 'natal sex', or 'actual sex'. If chromosomal, gonadal, hormonal, or genital sex characteristics are discussed, these terms should be used[14].

Cisgender person (cis person)
A person whose gender identity matches the sex assigned at birth and who, unlike transgender people, does not experience gender incongruence[2].

Gender binary
A view that there are only two genders (girls and/or women and boys and/or men) that are separate and unchanging[3].

Gender-affirming treatment
Medical treatments aiming to alter the bodily characteristics in order to align with the person's gender identity and ease gender dysphoria. Examples of gender-affirming health care include hormone treatments, hair removal, vocal training, and gender-affirming surgery[29].

Gender-affirming surgery
Range of surgeries that create physical characteristics that are in line with gender identity, including vaginoplasty, breast augmentation, cricoid surgery, vocal cord surgery, chest surgery, and phalloplasty. Sometimes referred to as sex reassignment surgery (SRS)[292].

Gender dysphoria
Distress caused by gender incongruence[2,29].

Gender Dysphoria
Refers to the diagnostic term in DSM-5 (REF.[156]). The diagnostic criteria includes male, female, and other gender.

Gender Identity Disorder
Refers to the diagnostic term in DSM-IV and DSM-IV-TR[293,294].

Gender nonconforming
This term refers to people who do not conform to society's expectations for their gender roles or gender expression. Another term used for this is 'gender-variant'[292].

Gender normative
Gender roles and/or gender expression that matches social and cultural expectations.

Gender transition
A person's adoption of characteristics that they feel match their gender identity. Gender transition can involve social, physical, and legal aspects of transition. Social transition includes changing appearance (including styles of dress and hair), name and pronoun. Legal gender recognition includes change of legal gender and arranging new identity documents. Physical transition can facilitate social transition and includes gender-affirming medical interventions such as hormone therapy and gender-affirming surgery[2].

Gynephilic
A sexual orientation towards women or femininity[81].

Legal gender recognition
The process by which a person's legal gender is changed to align with the person's gender identity[29].

Sexual orientation
Describes to whom one is sexually attracted. The sexual orientation of transgender people should be defined by the individual, and is often described based on the lived gender. A transgender woman attracted to other women would be a lesbian, and a transgender man attracted to other men would be a gay man[2,14].

Sex reassignment
Denotes the process to make a social, legal, and physical gender transition[292].

Sex reassignment surgery
See gender-affirming surgery[292].

Transfeminine
This umbrella term describes people who were assigned male at birth, who are transgender, and whose gender expression leans towards the feminine[29].

Transmasculine
This umbrella term describes people who were assigned female at birth, who are transgender, and whose gender expression leans towards the masculine[29].

Transgender person (trans person)
An umbrella term that describes a wide range of people whose gender and/or gender expression differ from their assigned sex and/or the societal and cultural expectations of their assigned sex[2,295].

Transgender man (trans man)
Denotes someone with a male gender identity who was assigned female at birth[2,295].

Transgender woman (trans woman)
Denotes someone with a female gender identity who was assigned male at birth[2,295].

Transsexualism
Refers to the diagnostic term in ICD-10 (REF.[157]). Transsexualism was also the word Harry Benjamin[23] used to describe individuals who felt that they had a gender identity not in line with their body and needed gender-affirming treatment. Both Benjamin and the ICD-10 diagnosis only acknowledge two genders: male and female.

forms of gender-affirming medical or surgical treatment. Considerations for treatment — both of underlying dysphoria and of any pre-existing or resulting sexual dysfunctions — are also discussed.

The biopsychosocial model

Sexuality and sexual response are complex and, as such, many models of sexual response have been suggested. The linear physiological model describes a response cycle in which individuals progress stepwise from desire, to arousal, to orgasm[45,46]. The dual control model or the sexual tipping point model are similar, and both describe how different biopsychosocial inputs influence sexual function. Thus, a sexual dysfunction occurs when inhibitory factors are not balanced by excitatory factor[47,48]. The incentive motivation model conceptualizes sexual response as an integration of central cognitive affective processes and peripheral responses. For example, perception of a genital response and/or feelings of sexual arousal motivate sexual behaviour and feelings of desire, leading to a rewarding orgasm[49,50]. This model also includes classical conditioning: a history of negative sexual experiences or a lack of positive experiences can alter a sexual incentive to a negative value. For example, if a person has developed severe genital dysphoria owing to gender incongruence, this discord could lead to orgasm being associated with negative feelings, hampering desire, arousal, and orgasm[51,52].

In the past, the aetiological background to sexual dysfunctions was thought to be either biological or psychological. This view has now been largely replaced by the biopsychosocial model (FIG. 1). In accordance with the biopsychosocial model, an assessment of sexual dysfunction should include an evaluation of predisposing, precipitating, and maintaining factors of all aspects of the model, including their interactions with one another[53]. This interaction means that problems in one domain — biological, psychological, or social — can negatively affect other domains.

Biological factors

On a physiological level, sexual function requires adequate hormonal stimulation, as well as sufficient cardiovascular, central, and peripheral nervous system function. Any process, including pharmaceutical drugs, affecting these systems or directly affecting the genitals might compromise sexual function: cardiovascular diseases mostly affect blood flow dynamics during the arousal phase[54]; neurological and psychiatric morbidity can compromise the autonomous, peripheral, and central nervous system and, therefore, also affect blood flow, sexual desire, and orgasmic ability[55]. Psychopharmacological drugs quite often have sexual side effects. Selective serotonin reuptake inhibitors (SSRIs) used for the treatment of depression and anxiety disorder can diminish desire and arousal and delay orgasm and/or ejaculation[56] Likewise antipsychotic drugs used for psychotic and bipolar conditions are well known for their adverse effects on desire and arousal. Opioids, which are sometimes necessary for the treatment of severe pain, suppress the gonadal axis in both men and women[57,58] and can suppress both sexual desire, arousal and orgasmic ability[59]. Studies investigating sexual side effects of pharmaceuticals have been performed on presumed cisgender persons; but it is likely that transgender persons do not differ from cisgender persons in this respect. Diseases or surgery involving the genitals, such as stress urinary incontinence, lichen sclerosis, or prostatectomy, can also negatively affect arousal, orgasmic ability, and sexual desire[60–63].

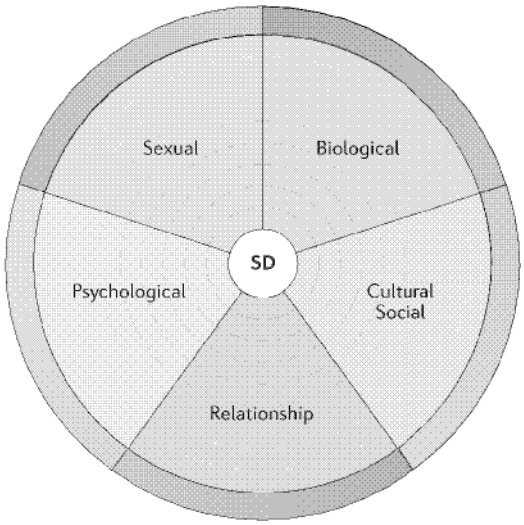

Fig. 1 | **The biopsychosocial model.** Sexual dysfunction (SD) should be understood as a multifactorial problem, with interacting contributing factors. Figure adapted with permission from REF.[53], Elsevier.

Psychological, social and sexual factors

Depression, anxiety, and other mental health problems often suppress desire and arousal, as well as the orgasmic ability[64]. On an intrapersonal psychological level, body satisfaction, body image, self-esteem, self-efficacy, coping strategies, age, and sexual scripts can all have an effect on sexual function and sexuality[53,65].

Sexual scripts — a set of cognitive schemas used to understand and organize sexuality and sexual behaviour[66,67] — are relevant on both intrapersonal and interpersonal levels, as well on as a cultural level, and all levels are interwoven. Cultural sexual scripts are part of the narratives and norms in each society, and provide guidelines regarding whether a sexual behaviour is considered appropriate, for example regarding numbers of partners, ways of having sex, reasons for having sex, and with whom[66,67]. The sexual scripts regarding transgender people are contradictory: where one script might describe transgender people as asexual[68], another script can objectify and sexualize them[44,69]. Sexual activity does not require a partner, but when a partner is involved, interpersonal factors also become a part of the biopsychosocial model. Interpersonal factors, which arise from either the relationship itself, the partners' sexual function, or the wish for being in a relationship, are likely to affect both sexual function and the person's own sexuality[53]

In order to understand and treat sexual dysfunction, a person's sexual history — including when they began masturbation and/or partner-related sexual activity, positive and negative sexual experiences, view of sexuality, sexual scripts, knowledge about sexual functions, importance of sexuality, and the presence of coexisting sexual dysfunctions — must be assessed. For instance, low desire can cause arousal problems and vice versa[60,70].

Hormonal control of sexuality and function

Endocrine factors are essential for reproduction and sexuality, and sex steroids in particular have specific effects on sexuality and sexual response. The terminology, which uses the terms 'male' and 'female' to describe sex hormones, is — to some extent — misleading, as both testosterone and oestrogen are present in both sexes and can work synergistically (for example, in bone[71] and in the brain[72]), as antagonists (for example, in breast[73] and body hair development[74]), or separately (for example, their effects on sex hormone binding globulin (SHBG) production)[75,76]. Notably, oestrogen levels in postmenopausal women are lower than in men of similar age[77–79]. Most of our knowledge of sex hormones in humans is derived from cisgender persons by studying states of hormone deficiency and restoration of normal sex hormone levels[80]. To what extent this information is transferable to transgender persons is not fully understood.

Disorders of sexual development of various kinds can affect development during the embryonic and fetal period and also during childhood and adult life, and have implications for the role of hormones in developmental

processes and also sexual preferences. For example, studies have shown that gynephilia (sexual orientation towards women or femininity)[81] is considerably more prevalent in women with congenital adrenal hyperplasia (CAH) than in women from a reference population without CAH, indicating a possible prenatal effect of elevated androgen levels on sexual behaviour[82,83]. Androgens are often referred to as 'sex-stimulating hormones', affecting spontaneous interest in sex, ease of arousal, and orgasmic experience[84]. They are also well known to influence sexual desire, with low sexual desire observed in men with hypogonadism restored by testosterone treatment in the same group[85,86]. In cisgender women, the relationship between testosterone levels and sexual desire is less clear[87], although intervention studies in cisgender women with low sexual interest and sexual dysfunction demonstrate a positive effect of testosterone therapy on sexual activity, orgasm, and desire, as well as improvements in general sense of well-being and self esteem[88–90].

One randomized, controlled study has shown that the effect of testosterone treatment on sexual desire in hypogonadal cisgender men is reduced if an aromatase inhibitor (which reduces oestrogen levels) is administered simultaneously, suggesting a synergistic or additive effect of oestrogen on male sexual desire and erectile function[79]. In cisgender women, the role of oestrogen in sexual desire is unclear, with conflicting reports. Sexual desire and frequency of sexual fantasies decrease following oophorectomy[91] and oestrogen treatment can increase desire and orgasm in oophorectomized women[92]. Furthermore, addition of testosterone to hormone replacement therapy (HRT) in oophorectomized and in postmenopausal women further improves sexual function[93,94].

Hyperprolactinaemia is associated with loss of sexual desire in cisgender men even if the testosterone levels are normal[95]. In cisgender women, excess prolactin levels due to lactation or a prolactin-producing tumour cause amenorrhoea and diminished sexual interest. This effect could be considered functional, as it lowers the chance or risk of becoming pregnant too early in women who are caring for a newborn. Furthermore, sexual activity and orgasm release a series of neurotransmitters and hormones, such as oxytocin, that might be involved in the positive experience of having sex[96].

Thus, the role of hormones in controlling and maintaining sexual function and desire illustrates the biopsychosocial model, whereby a biological factor (hormones) controls psychological factors (for example, desire and fantasy), which in turn modulate social factors (relationships and sexuality). Understanding the balance of the biopsychosocial model can, therefore, inform effective treatment of transgender individuals, and those with gender dysphoria.

Pretreatment sexuality in trans persons

Body image and body dysphoria

A negative body image and low body satisfaction is more prevalent in transgender individuals who apply for gender-affirming treatment than in cisgender persons, as body dysphoria is one of the core elements of gender dysphoria[97].

Qualitative studies describe difficulties among individuals with gender dysphoria to be nude alone or with a partner and difficulties of touching one's own body or letting somebody else touch it, with a greater focus on satisfying a partner[43,44,98]. Body satisfaction is dependent on the degree of body and genital dysphoria, but also on coping strategies to handle the dysphoria[99]. Thus, some individuals use coping strategies such as imagining a different body, reinterpreting gendered body parts, or applying a gender role during sex congruent with their gender identity[42]. Studies have shown that gender-affirming treatment by itself increases body satisfaction[40,42,97,100–102]. However, paradoxically, accepting a need for gender-affirming treatment, disclosing a transgender identity to others, or beginning a medical and surgical gender-affirming treatment, can transiently increase body dysphoria and body dissatisfaction[40,43]. This phenomenon might exist because denial or neglect of the dysphoria is a coping strategy that is no longer possible when the person starts coming out for themselves and others, and when they begin to be asked questions about feelings of body incongruence by a health-care professional[103].

Sex, relationships, and orientation

Sexual experience, function, and satisfaction before gender-affirming treatment are likely to also influence sexuality and satisfaction after treatment. A vast majority (80–92%) of persons applying for gender-affirming treatment or those who had unmet gender-affirming treatment needs have, in the past, been sexually active with a partner[40,104]. However, only half of this group engaged their genitals in sexual activity, and only 12% of transgender women and 15% of transgender men in this group derived pleasure from involving their genitals in sexual activity[104]. Masturbation was reported by 72–78% of transgender women and 59–89% of transgender men[40,104]. Furthermore, in one study, 40% of transgender individuals with unmet gender-affirming health needs reported sexual dissatisfaction, even though sexuality was reported as important by 47% of the transgender women and 57% of the transgender men[40]. Previous traumatic sexual experiences with partners, friends, or unknown persons in childhood or adulthood are more prevalent in transgender persons than in the cisgender population[44,105–107]. Historically, some studies have suggested that childhood sexual abuse experience might be implicated in the aetiology of gender incongruence[108,109], whereas more recent papers have argued that minority groups are more vulnerable to sexual abuse[110–112]. Traumatic sexual and other experiences are certainly associated with increased psychiatric morbidity and render the person more vulnerable[113,114]. Sexual orientation is multidimensional, comprising sexual identity (self-labelling as gay, straight, bi, or other), sexual behaviour (whom you have sex with), and sexual attraction (to whom you feel attracted or fantasize about)[115]. The different dimensions are not always congruent; that is, some cisgender men have sex with cisgender men but are at the same time in a relationship with a cisgender woman and identify as straight[115].

Gender dysphoria is not related to sexual orientation and transgender individuals express the whole spectrum of sexual orientations — androphilic (sexual orientation towards men or masculinity), gynephilic, bisexual (sexual orientation towards both men and women), pansexual (sexual orientation towards individuals irrespective of sex or gender), asexual (sexual orientation towards no one and /or low sexual motivation and desire)[116], or queer[6,19]. Furthermore, sexual orientation in transgender persons can be fluid and dynamic, and can change during transition[19,104,117,118].

A multitude of factors, including access to a partner or partners, apart from or together with preferences, are important determinants in sexual satisfaction and might not be congruent with sexual behaviour. For example, a transgender woman attracted to men might be in a relationship with a cisgender androphilic man, which can influence her level of sexual satisfaction[44,104,119]. Transgender men and women can be in a relationship in line with their sexual orientation or not; transgender women are more often in a relationship not in line with their sexual orientation than transgender men[119]. Irrespective of gender, sexual relationships not in line with a person's sexual orientation involved less sexual activity using the genitals[119].

Many transgender persons find it difficult to establish a new relationship — whether sexual or not — both before and after gender-affirming treatment, sometimes owing to difficulties in finding a partner who respects them and views them according to their gender identity without objectification[44,104,119]. One study reported that 53% of transgender men and 37% of transgender women who sought treatment answered positively when asked if they had a current partner[119], but it must be borne in mind that having a partner might delay the coming-out process for those who fear losing their partner[120].

Sexuality and gender-affirming treatment

Effects of hormonal therapy

The goal of endocrine feminizing treatment in transgender women is to increase oestrogen to the levels observed in premenopausal mid-cycle cisgender females (400–800 pmol/l) and to suppress androgen-dependent pathways in order to induce the desired physical and mental changes. This effect is achieved with oral, transdermal, or intramuscular administration of oestrogen[80]. Oestrogen suppresses gonadotropin secretion and, therefore, testosterone production and secretion from the testis. In order to further suppress testosterone, gonadotropin-releasing hormone (GnRH) analogues or gestagens, such as cyproterone acetate or medroxyprogesterone, are often added[80]. Gestagens exert dual effects, suppressing testosterone production and blocking the androgen receptor (AR)[121]. The result of testosterone suppression is a change in body composition with increased fat mass, decreased muscle mass, initiation of breast development, softened skin texture, and reduced body hair[80]. Spontaneous and nocturnal erections usually disappear, semen production and spermatogenesis ceases, and ejaculate volume decreases, suppressing fertility[80].

Conversely, the goal of endocrine masculinization treatment in transgender men is to stimulate androgen-dependent pathways by increasing testosterone and suppressing oestrogen levels to the normal range for healthy cisgender males (50–180 pmol/l) and thereby induce the desired physical and mental changes[80]. Testosterone is administered transdermally (50–100 mg daily) or by intramuscular or subcutaneous injections (~100 mg per week), suppressing gonadotropin secretion and, therefore, oestrogen production from the ovaries and inducing physical changes including increased muscle mass, decreased fat mass, increased facial and body hair growth, increased risk of male-pattern hair loss, growth of the clitoris, and a deepening voice[80]. Furthermore, testosterone treatment usually induces a reduction in vaginal lubrication and cessation of menses, owing to the suppression of gonadotropins[80]. If cessation of menstrual periods does not occur, gestagens or GnRH analogues can be added[80]. Fertility is also suppressed while on treatment.

In general, androgen treatment in transgender men results in increased sexual desire and, eventually, improved sexual satisfaction. Endocrine treatment of transgender women reduces sexual desire and — depending on the patient's wishes to either maintain desire and/or erectile function or to experience lower desire and/or fewer erections — satisfaction with treatment varies[80]. After endocrine therapy, when nocturnal and spontaneous erections decrease in frequency and intensity, erections arising as a result of sexual stimulation seem more persistent[122].

For young people who have not yet gone through puberty, GnRH analogues can be used to arrest pubertal development, with the goal of suppressing development of unwanted bodily features and gain time for investigation and consideration of further intervention[123].

Endocrine therapy can also have effects on pain, and changes in pain perception due to endocrine treatment in transgender patients are of potential importance, but are not well studied. In the general population, the prevalence of chronic pain is higher among women than men[124] and several experimental animal studies have suggested that testosterone administration increases the pain threshold[125–128] whereas oestrogen lowers it[128]. Accordingly, some human studies have found that endogenous and exogenous testosterone reduces pain[129,130]. In a retrospective report, ~25% (11 of 47) of transgender women developed chronic pain concomitantly with oestrogen and/or antiandrogen therapy, whereas 60% (6 of 10) of transgender men reported a significant improvement in chronic headache that had been present before the start of testosterone treatment[131]. Although in these studies the investigated pain was not specifically related to sexual activity, the findings should motivate further study to elucidate the roles of cross-sex hormones in sexual pain, whether in cisgender or transgender persons.

Effects of gender-affirming surgery

Some individuals experiencing gender dysphoria request GAS in order to align their physical gender with their gender identity and ease their dysphoria[132].

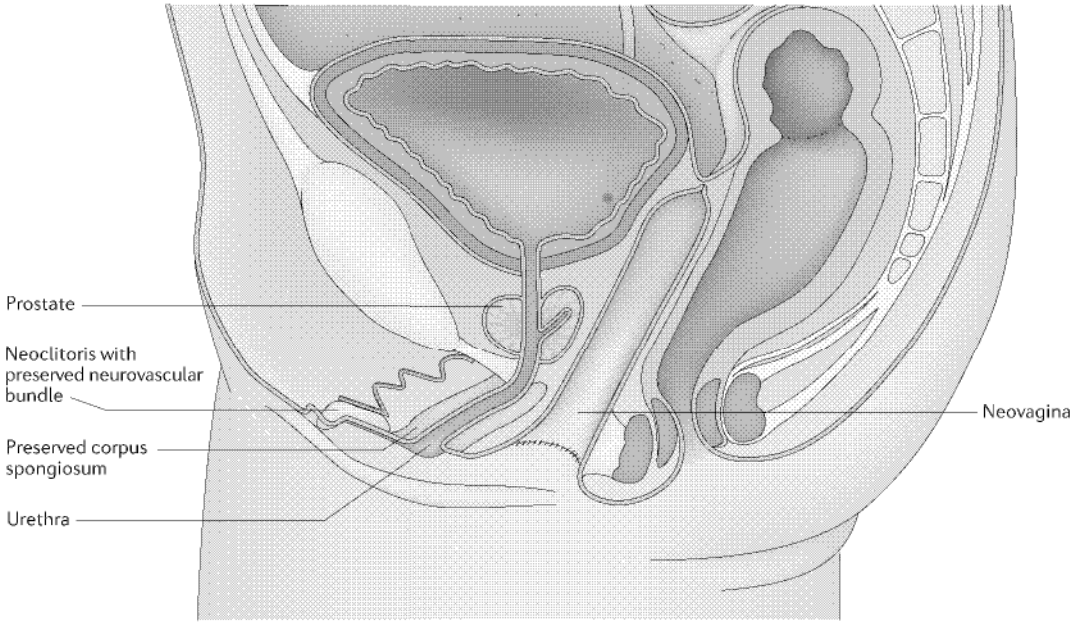

Fig. 2 | **Vaginoplasty.** A neovagina is formed in the space between the urethra and rectum. The corpus spongiosum is preserved and surrounds the urethra. A small piece of the glans penis is preserved, embedded, and formed to become the neoclitoris. From the dorsal side of the penile shaft the thin neurovascular bundle is preserved and buried below the neoclitoris to ensure vascularization and erotic sensitivity. The prostate shrinks with antiandrogen treatment. The space between urethra and neoclitoris can be covered with urothelium in order to enhance sensitivity.

Feminizing genital surgery for transgender women consists of removal of the penis and the gonads and creation of a vagina, labia, and clitoris (FIG. 2). Several vaginoplastic techniques are in use, the most common of which is the penile skin flap technique, whereby the skin of the penis, if sufficient, is inverted to form the vaginal wall. The anatomy of the male perineum and pelvis leaves a space between the prostate and rectum that enables formation of a neovagina. In order to maintain the new vagina and to ensure its persistence and suitable size for penetration, daily dilatation (vaginal dilators and/or vaginal sex) is usually needed, dependent on the surgical technique used[133]. Alternatives to penile skin for creation of a neovagina include scrotal skin, free skin grafts, or bowel segments[134]. The glans penis can be used for formation of a neoclitoris, with reasonably preserved genital sensitivity and sexual responsiveness[135–138]; the scrotum can be used to create the equivalent of labia majora. Feminizing surgery also often involves cricoid surgery, vocal cord surgery, breast augmentation, and facial feminizing surgery. Breast augmentation, in particular, has been shown to increase sexual well-being in transsexual women[102].

Masculinizing genital surgery in transgender men can include removal of the uterus and ovaries and optional vaginectomy, as well as creation of a neophallus. Two methods are generally used to create a new penis or a penis-like structure. For phalloplasty, a flap from the inguinal region, anterolateral thigh, or forearm is used to form the contours of a penis[139–144]. This type of neophallus lacks erectile properties, but erogenous sensitivity can be obtained through nerve anastomoses between flap nerves and the genitofemoral and clitoral nerves and via the clitoris, which is still present behind the neophallus[145] (FIG. 3).

Different donor sites are associated with corresponding differences in sensitivity and bulkiness. Several techniques are available for erection support, most of which involve a semirigid or inflatable prosthesis. An estimated 25% of transgender men who undergo phalloplasty receive a penile prosthesis[139]. All these techniques enable the possibility of engaging in penetrative sex, or, alternatively, a rigid condom or penile sleeve can be used.

A major achievement with phalloplasty is to enable voiding standing up. Among transgender men interested in phalloplasty, 62–99% stated that voiding standing up is a factor of high importance[146,147] and according to a meta-analysis, this was achieved in 73% of subjects[148]. In one study on genital confirming surgery in transgender men, 45% reported a strongly improved ability to void standing, although no effect on quality of life was reported[132]. Metoidoplasty is an alternative method used for creation of a penis in transgender men, which is facilitated by use of the testosterone-enlarged clitoris, whereby the visible part of the clitoris is further enlarged by luxation of the crura clitoris from its internal support. Compared with phalloplasty, metoidioplasty creates a smaller penis with maintained erectile properties and erotic sensitivity, although usually insufficient for full penetration due to inadequate length[149] (FIG. 4). Transgender men who have undergone metoidioplasty might subsequently request phalloplasty[150,151]. In both procedures, the labia majora are used to create a scrotum large enough to harbour testicular prostheses[134,139]. Nongenital masculinizing surgeries include liposuction

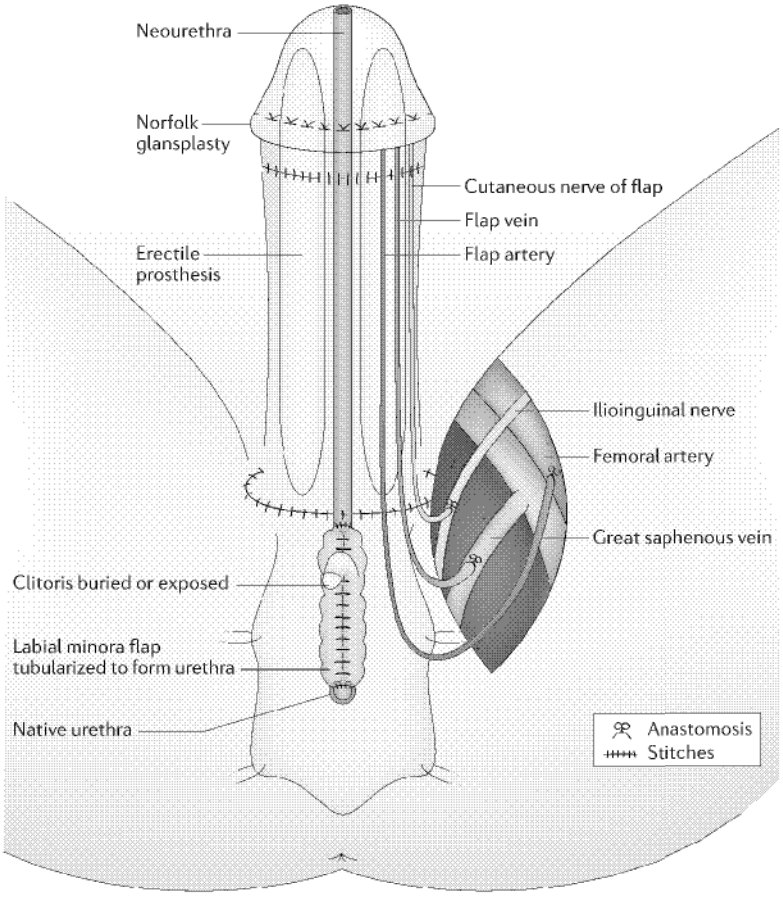

Fig. 3 | **Phalloplasty technique.** A flap from the inguinal region, anterolateral thigh, or radial forearm is formed to the neophallus. Vascularization and sensitivity is ensured by anastomosis with existing vessels and nerves. A sensitive clitoris is preserved and can be buried or exposed. For erection, a semirigid or inflatable prosthesis can be inserted in the neophallus, and scrotoplasty, including testicular prostheses, is also an option.

and mastectomy, and a few studies have evaluated effects of these techniques on sexuality. In a 2018 study of natal females aged 13–25 years with chest dysphoria, 50–60% of those who had not undergone mastectomy reported problems with dating, forming intimate relationships, physical intimacy, or sexual activity, compared with just 2–3% in the group who had undergone surgery[152]. One study has also reported a statistically significant positive effect of mastectomy on satisfaction of life in general and on feelings of self-worth[153], but no statistically significant improvement has been shown in pleasure of sexual activities, sufficiency as a sexual partner[153], or sexual quality of life[154].

Overall, the individual's sexual wishes and hopes are important parts of surgical decision-making[132], regardless of whether the patient is a transgender woman or a transgender man, or the type of surgery they seek.

Sexuality and access to care

Access to care and financing of medical care varies both within and between countries[2]. Eligibility criteria vary and contribute to differences in access to care. In some countries, the inclusion criteria for treatment exclude transgender persons who would be eligible for treatment in other countries. When treatment of gender identity became available in the mid-1960s, eligibility criteria were stringent and patients could be considered ineligible for treatment for a number of reasons that today are irrelevant, including high levels of sexual activity, homosexuality, and also being aroused by cross-dressing[16,21,22,155]. The gradual change from rather exclusive criteria to a more inclusive approach is still not fully integrated into clinical management. This lack of integration might hamper conversations about sexuality and sexual function between health-care providers and patients, as patients can fear being considered ineligible for gender-affirming care.

Post-treatment sexuality

Although the affirmation of gender by hormonal and/or surgical treatments could be considered the final step in managing the transgender patient, it does not necessarily provide a solution for sexual dysfunctions and, in fact, marks the beginning of a new life in which their sexuality and sexual health could require considerable support. On a purely biological and physiological level, hormonal therapy and surgery can have long-term effects on sexual function, while the reality of changing gender can have considerable psychological and social effects, which can also substantially affect sexuality and sexual function, according to the biopsychosocial model.

Desire

Sexual desire can be defined as the urge, drive, or lust that motivates us to engage in sexual activity, alone or together with someone else, and comprises sexual drive (biological), sexual motivation (cognitive) and responsiveness to stimuli[34]. The strength of this desire varies between individuals, particularly if a distressing dysfunction is present. A low level of desire might fulfil the criteria for a medical diagnosis such as hypoactive sexual desire disorder[156], whereas a high level of desire might fulfil a diagnosis of hypersexuality[157]. Gender differences in sexual desire are well recognized, with cisgender men generally reporting more intense and more frequent desire than cisgender women[158,159].

Sexual desire in transgender women. Gender-affirming treatment affects sexual desire in a majority of transgender women[160]. Retrospectively, 70% of the transgender women in one study self-reported a lower or much lower sexual desire ($P<0.001$) after gender-affirming treatment, compared with sexual desire before gender-affirming treatment[160].

Some transgender women report no change or even increased desire[160]. The effect of hormone treatment seems to be quite prompt, with ~60% of transgender women reporting low sexual desire 3 months after the initiation of hormonal treatment, compared with ~30% before hormonal treatment[161].

Low sexual desire should not necessarily be assumed to be a problem for the majority of transgender women, especially in the presence of strong genital aversion, and if vaginoplasty is not imminently available. In fact, it has been reported that only one in three transgender women

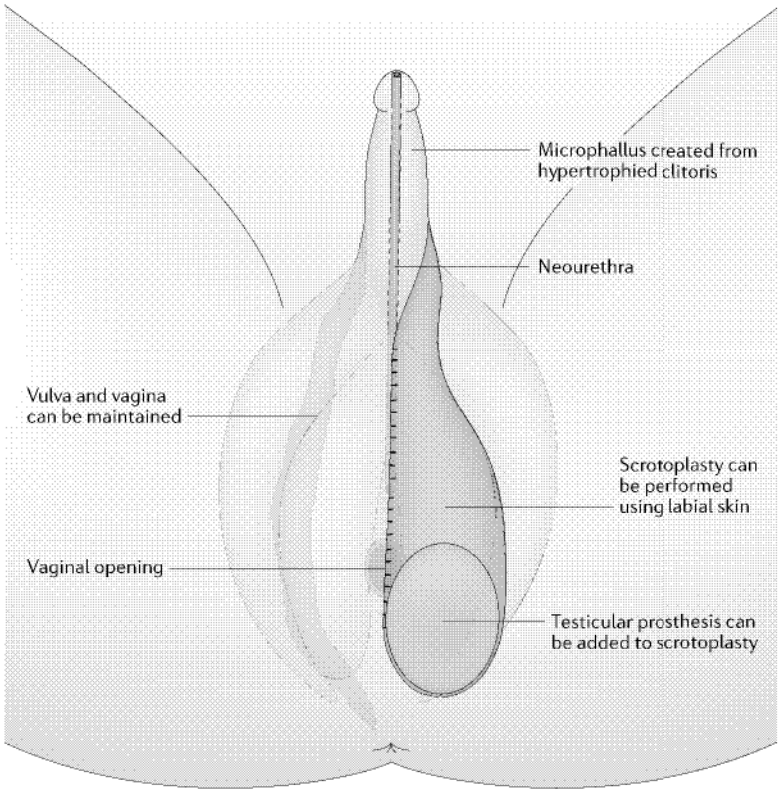

Fig. 4 | **Metoidoplasty.** A microphallus with preserved sensitivity and erectile ability is created from the androgen-enlarged clitoris. Scrotoplasty, including testicular prostheses, is an option.

considered low sexual desire distressing[160]. A low sex drive can, therefore, be seen as a relief and can even be supported in clinical practice by provision of sex-drive suppressing medication.

The timing of the decrease in sexual desire after initiation of hormonal treatment together with the fact that testosterone levels are known to influence sexual desire in men[95] suggests that reduced desire would be precipitated by reduced testosterone levels caused by antiandrogen therapy. One study showed significantly lower levels of total and calculated free testosterone (cfT) in transgender women compared with a control group of ovulating cisgender women (T: 20.0 ± 9.6 ng/dl versus 33.9 ± 7.9 ng/dl, $P < 0.001$; cfT: 0.26 ± 0.16 ng/dl versus 0.47 ± 0.31 ng/dl, $P < 0.001$)[162]. Nevertheless, no studies have shown any significant correlation between levels of total or free testosterone and sexual desire in transgender women[160,162,163].

For some transgender women, low sexual desire can lead to personal or relational distress, fulfilling the diagnostic criteria for hypoactive sexual desire disorder (HSDD). Two studies have examined the prevalence of HSDD in transgender women compared with cisgender women using the Sexual Function Health Council's consensus definition[33]. Both reported that the prevalence of HSDD in transgender and cisgender women were similar, at 20% in transgender women compared with 27% in middle-aged women[164] and 26% in younger, surgically postmenopausal women[165] in one of the studies[160], and 33% in transgender women compared with 23% in a control group of ovulating women and 26% in middle-aged women[166] in the other study[160,162].

Whether surgical treatment for transgender women enhances or reduces sexual desire is not known. One study compared desire in transgender women after vaginoplasty with transgender women on the waiting list for surgery, and showed that those who had undergone surgery reported higher sexual desire than those who had not, suggesting that gender-affirming surgery might have a positive effect on sexual desire[160]. This effect is likely to be due to improved body satisfaction. Seven publications[163,167–172] have used the standardized female sexual function index (FSFI) questionnaire — which was developed and validated for penetrative sex in cisgender women — to evaluate desire in transgender women, including assessment of desire, arousal, lubrication, orgasm, satisfaction, and comfort[173,174]. In these studies, the transgender women's average score in the 'desire' subdomain was comparable to that of cisgender women without sexual problems[163,167–172].

When considering sexual desire in the transgender population, it should be borne in mind that few studies on transgender sexuality after gender-affirmative treatment have evaluated the prevalence of depression and the use of pharmacological treatment with sexual side-effects among the participants, despite the fact that 25% of the included transgender women in one study were treated for depression[175].

Sexual desire in transgender men. Just as in transgender women, gender-affirming hormone treatment affects sexual desire in most transgender men[118,176–178]. Several studies have examined changes in sexual desire after initiation of testosterone treatment but before gender-affirming genital surgery, and unanimously describe a trend towards increased sexual desire after testosterone therapy[118,176,177], which is also described as more urgent, less controllable[118], and more frequent[176]. As in transgender women, the effect of gender-affirming hormone therapy on sexual desire occurs soon after treatment, within 3 months of initiation of endocrine treatment[161]. However, even though a majority of transgender men report increased sexual desire, a small percentage of transgender men remain unaffected and, in one prospective study, ~10% reported reduced desire after gender-affirming hormone treatment[176]. In this specific study, other possible confounders causing low desire, such as disappointment with bodily changes due to the use of relatively low doses of testosterone, were not taken into consideration.

In transgender men, no association has been reported between total or free testosterone and sexual desire[176,177]. However, the level of luteinizing hormone (LH), which reflects testosterone levels, has been negatively associated both with solitary and dyadic sexual desire[177], indicating a connection between desire and the pituitary–gonadal axis. The relationship between LH and desire in transgender men is likely to resemble that of cisgender men, but there might also be differences, such as different embryonic and/or neonatal priming of the male and female brain.

One study has examined the prevalence of HSDD in transgender men and reported a rate of 5%, which is comparable to the general cismale population[160]. In the same study, a level of increased sexual desire that caused personal or relational distress was reported by 3.6% of the transgender men[160]. The prevalence of hypersexuality in cisgender men is estimated to be 2–6%[179–181], although a comparison with transgender men is not meaningful owing to the lack of information about compulsiveness in transgender men and of a generally accepted diagnostic definition of hypersexuality.

The combined effect of both testosterone treatment and genital surgery on desire has been investigated in 45 transgender men, 8 years after gender-affirming phalloplasty[177]. In this retrospective study — one of only a few studies that used a validated scale for measurement of sexual desire, The Sexual Desire Inventory (SDI) — 73% of trans men reported much higher or increased sexual desire after surgery, and 25% reported no difference. No specific information has been reported regarding effects of surgery alone on sexual desire, but one interesting finding is that postoperative desire in men who had undergone phalloplasty with an erection prosthesis did not differ from those without an erection prosthesis[177]. Furthermore, satisfaction with the surgery did not influence desire[177]. These data indicate that surgical outcome is not the only relevant predictor in sexual functioning after gender-affirming treatment. In another study, just 12% of trans men reported reduced desire following gender-affirming treatment with hormones (100% of participants) and surgery (85% of participants)[160], which is in stark contrast to the high numbers (>70%) of trans women who report reduced desire after treatment.

Sexual arousal

Sexual arousal refers to both the subjective feeling of arousal and the physiological response that occurs with sexual activity. This response includes increased heart rate and respiratory frequency, accompanied with increased blood flow to and swelling of the genitals resulting in penile erection or clitoral engorgement, and, in women, vaginal lubrication. In natal females, vaginal lubrication comes from Bartholin's glands and Skene's glands and from increased blood flow in the vagina, which results in exudation of fluid[182]. Lack of genital arousal and lubrication for both cis and trans women, and for transgender men who choose to retain their vagina, can cause discomfort or pain during vaginal sexual activity. The subjective experience of sexual arousal can be measured by validated questionnaires, and objective measurements can be taken using plethysmography[183], which assesses vaginal vasocongestion, or laser Doppler imaging[184], which measures vulvar blood flow, and functional MRI (fMRI)[185–187] for brain activity. Notably, subjective and objective arousal are not always concordant[188].

Not all transgender persons want, need, or can even afford to undergo gender-affirming genital surgery[2,15,118,189]. As a consequence, the genital effect of hormonal therapy in each individual depends on which genital organ is, or is still, present.

Sexual arousal in transgender women. For transgender women with a penis, the physical sexual arousal phase includes the ability to achieve and maintain penile erection. Erectile ability is, to some extent, dependent on intermittent increases in penile blood flow with increased oxygenization, which usually occur as nocturnal tumescence and erectile episodes, which are testosterone dependent[87]. One study has examined the effect of androgen depletion on erection in transgender women who retain their penis, and found no difference in patient-reported outcomes before and after cross-sex hormone treatment, although the frequency of nocturnal erections, measured with a Rigiscan on two consecutive nights, were reduced in almost half of the transgender women. The result of the nocturnal penile tumescence test also correlated ($P = 0.006$) with serum testosterone levels. These data support the existence of androgen-dependent nocturnal erections in transgender women who retain their penis[122]. Studies in cisgender men have shown that reduction in nocturnal erections is a risk factor for development of penile fibrosis and erectile dysfunction[190]. For transgender women who wish to maintain erectile ability, occurrence of nocturnal and spontaneous erections might, therefore, be important, and can be supported by low-dose testosterone and/or the use of phosphodiesterase type 5 (PDE5) inhibitors[191].

Experimental studies have examined sexual arousal in transgender women with a neovagina using vaginal photoplethysmography to measure vaginal blood flow[192–194] or fMRI to examine cerebral activity[185,186] at baseline and while watching an erotic video[185,186,192,194]. The results of these studies demonstrate several similarities between transgender and cisgender women. Baseline waveforms of vaginal pulse amplitude (VPA) in trans women were comparable to that of cisgender women[193], and transgender women's subjective arousal correlated with their vaginal arousal as well as, or better than, that of women in a cisgender comparison group[194]. Brain activation patterns associated with visual sexual stimulation in transgender women were similar to those observed in premenopausal cisgender women[186]. However, differences were noted in vaginal photoplethysmography response during neutral stimuli in trans women, with a stimuli response that was substantially smaller than that of the cisgender women[194]. This discrepancy is most likely due to anatomical differences, such as the higher vascularization and innervation of the cis vagina than the neovagina[194].

Subjective arousal in transgender women has been investigated in a series of studies and all report that a majority of trans women were able to experience arousal[163,167–170,175,192]. The average FSFI subdomain score for arousal in transgender women mostly resembles that of cisgender women with sexual problems[163,167–172] such as low desire or pain[173]. Somewhat contrary to the reported decrease in sexual desire, one study has also found an increase in subjective arousability following gender-affirming treatment[175].

One study has reported that the ability to experience arousal after gender-affirming surgery might require a lag time of up to 6 months[168]. Although physical recovery from surgery is a factor, this lag might also be due

to additional factors, such as adapting to the changed body and paused sexual activity while this adaptation takes place[44].

Several studies have reported that neovaginal lubrication is not only possible but that the majority of transgender women experience vaginal lubrication after surgery[135,138,175]. However, despite the fact that many transgender women report lubrication during arousal, the skin that is commonly used to line the neovagina provides less moisture than a natal vagina, making use of lubricants a necessity during penetration and dilatation training[195]. Lack of lubrication is less frequent with use of the intestinal vaginoplastic technique than with the use of a skin flap technique[133,171], but might be complicated by side effects such as mucorrhoea[196,197] or stenosis at the anastomotic site[133]. Nevertheless, lack of arousal, lubrication, and pain are often reported as major concerns after surgery[138,163,167–170,198]. If only sexually active transgender women are included in the analysis, the reported levels of arousal and lubrication are more in line with cisgender women without sexual problems[167,168]. However, many trans women are not sexually active; celibacy in this population might be due to lack of arousal, lubrication, pain, or a lack of desire, or other unknown reasons, but no studies have been carried out to investigate this situation.

Sexual arousal in transgender men. Transgender men, just like transgender women, do not always undergo GAS[2,15,189,199]. In a long-term study from Amsterdam including 1,401 patients, 39% of transgender men underwent phalloplasty and 76% of transgender women underwent vaginoplasty. Thus — as in transgender women — the transgender men's sexual situation will differ according to the genital organs present. Sexual arousal in transgender men has received little attention beyond the subjective experience of feeling aroused. In transgender men with a vagina, physical sexual arousal in the genital sense of the word mainly is influenced by a thinning of the vaginal epithelium caused by androgen treatment[200]. This vaginal atrophy is known to cause vaginal dryness and dyspareunia in naturally[201] and surgically postmenopausal[202] cisgender women.

Self-reported sexual arousability has been examined prospectively before and after 1 year of hormonal therapy[176]. This study reported significantly increased frequency of desire ($P=0.0014$), masturbation ($P=0.0001$), sexual fantasies ($P<0.0005$), and arousal ($P<0.0005$) after 1 year of testosterone administration[176]. These data are also supported by a retrospective study reporting a significant increase in frequency of masturbation ($P = 0.023$) after hormonal treatment[175].

No objective method is able to measure penile sexual arousal in phalloplasty patients in whom erection is accomplished with a bone graft or a prosthesis as, in these patients, erection is not arousal dependent. Regarding arousability, the natal clitoris is modified and left in place behind the neophallus, usually with preserved sensitivity[145]. One of the clitoral nerves is sometimes used to enable development of sensitivity in the neophallus[136,203]. Between 50–100% of men who have undergone GAS have reported experiencing erogenous sensation in the neophallus[203–205], with the exception of one study that reported obvious erogenous sensation in only 9% on tactile stimulation, although 83% had functioning sensory sensitivity[206]. This seemingly contradictory report could possibly be explained by differences in questionnaires being used.

Metoidioplasty produces a smaller penis than phalloplasty but, in the majority of patients, it is capable of a physiological erectile response[149,207,208]. However, anatomical differences in the penile and clitoral size and structure mean that it is seldom possible for this erection to be used in penetrative sex[149,207], although one study claimed intromission was possible for 70% of patients in their metoidoplasty cohort[208].

Orgasm

Orgasm, or climax, denotes the highest point of sexual excitement, characterized by feelings of pleasure and accompanied by pelvic contractions and ejaculation or increased vaginal lubrication. Orgasm can be achieved through penile or clitoral stimulation as well as through stimulation of other erogenous zones including the prostate, anus, breasts, or nipples. Difficulty in reaching orgasm is commonly reported in cisgender persons, with 16% of women and 9% of men reporting anorgasmia in a British national survey[159]. Orgasm can be subjectively assessed using questionnaires such as the Brief Index of Sexual Functioning for Women (BISF-W)[209] or the FSFI[174], and can be objectively measured using fMRI[210], or — less commonly — positron emission tomography[211] or rectal pressure[212].

Orgasm in transgender women. The question whether transgender women are able to achieve an orgasm after vaginoplasty has been addressed in several studies. In the majority of these studies, 62–100% of transgender women with a neovagina reported orgasmic ability[133,136,171,175,193,213–227]. A few studies described cohorts with a lower prevalence of orgasmic ability (27–48%)[192,228–231], but many of these studies are small and are limited by selection bias, have not used validated questionnaires, include both sexually active and inactive transgender women, and are mostly retrospective and lack control groups. Overall, one can conclude from these studies that orgasm in postoperative transgender women is a possibility. As is the case in cisgender women, it seems to be easier for transgender women to reach orgasm during masturbation than in connection with partner-related sex[175].

Data suggest that a majority of transgender women experience a change in quality of the orgasmic feeling after surgery[175,215–217,219,220,227]. The 'new' orgasmic feeling has been described as more intense[175,219], smoother and longer[175], more pleasing[220] and more pleasurable[227] than the quality of their preoperative orgasms. However, vaginoplasty can also result in loss of orgasmic ability or experiencing less orgasmic sensation[167].

Several studies have also confirmed orgasm-triggered secretions in transgender women[135,175,193,220,227,232] — that is, the ability to ejaculate. The anatomical correlate to this is not clear but, in analogy with lubrication, it might involve the retained Cowper's glands[233] or the remaining prostate and seminal vesicles[234].

In transgender women who retain their penis, inadequate erection and ejaculatory difficulties as a consequence of low testosterone levels might be a concern[59].

Orgasm in transgender men. Transgender men's ability to orgasm is less well studied and has focused on *trans* men who have undergone phalloplasty or metoidioplasty. The effect of hysterectomy has not been studied in postoperative transgender men. Hysterectomy is not known to affect orgasm capacity in cisgender women[235].

In general, orgasm is reported to be possible for many transgender men regardless of whether they have undergone phalloplasty or metoidioplasty, although prevalence estimates vary from 25% to 100%[136,149,175,205,223,231,236,237]. Just as in transgender women, orgasm through masturbation seems to be more prevalent than through sexual intercourse[175,223].

No studies have specifically addressed orgasm in transgender men with a vagina. However medical interventions are unlikely to have a negative effect beyond the vaginal dryness that usually occurs as a result of oestrogen deficiency. Hypersensitivity of the enlarged clitoris can be an issue[137], but whether this affects orgasmic ability is unclear.

A change in orgasmic experience after endocrine and surgical treatment has been reported in most transgender men[175,223,237], and has been described as the orgasm being more powerful and shorter[175] or being more intense[237]. No difference in orgasmic feeling has been described between those patients who have undergone phalloplasty with or without a penile prosthesis[237].

Pain during sexual activity

Pain during sexual activity can be caused by a multitude of factors including insufficient arousal, surgical complications, or muscle tension[139,238,239]. Transgender men and women might be afraid of damaging their new organs, or have painful experiences from dilatation of the neovagina during the immediate postoperative rehabilitation, potentially leading to muscle tension and consequent pain[240]. In cisgender populations, pain during sexual activity is reported to occur in 1.8% of men and 7.5% of women[159,241] and, correspondingly, pain and lack of arousal and lubrication are reported as major concerns after surgery in transgender women, but prevalence data regarding these factors are unreliable[163,175,198,242]. These problems are associated with lower sexual satisfaction in both cisgender[238] and transgender populations[138]. The average FSFI subdomain for pain in transgender women is similar to that of cisgender women with sexual problems[173] such as low desire or pain[163,167–170,172], although a 2018 study of trans women who underwent pedicle transverse colon flap reported numbers that are more in line with cisgender women without sexual problems[171]. Complications after phalloplasty or metoidioplasty are generally more common than after vaginoplasty[139,150,243,244]. The report of pain during intercourse in >50% of men with an erection prosthesis is particularly concerning[175,237]. Pain during sexual activity in transgender patients that is not related to phalloplasty or metoidioplasty has not been studied.

Sex, relationships, and sexual orientation

Sexual activity, whether masturbation or partner sex, is generally reported to increase or remain unchanged in transgender men after gender-affirming treatment[160,175,176,245,246], but in one study, 11% of transgender men reported no masturbation after gender-affirming treatment[160]. For transgender women, some studies report increased or unchanged sexual activity[175,227,247,248] and others a decrease[245,246]. In cross-sectional studies, sexual activity with a partner or masturbation after GAS is reported in 50–89% of transgender women[40,198,227]; thus, 11–50% of trans women are sexually inactive after gender-affirming treatment. The numbers are similar for transgender persons who have unmet needs for GAS. Most studies are cross-sectional or retrospective, and few prospective studies have described the effect of GAS per se on sexual activity. One prospective study with a small sample of transgender women found that those who were sexually active before GAS remained so after treatment, and vice versa for the sexually inactive[228]. Most studies report that around 35–40% of transgender women and 40–75% of transgender men are in a relationship with a partner after transition[160,249–251] and the number of transgender men who reported being in a relationship did not change after treatment[176]. Satisfaction with partner relationships improves for both genders after gender-affirming treatment[175,249]. Initiating a new relationship can be difficult for trans persons both before and after gender-affirming treatment, and many trans persons report difficulty in finding a partner who is able respect them and see them according to their gender identity, who does not objectify them, and who can accept their level of sexual self-esteem and their sexual agency[44,104,119,176]. Research suggests that it can be more difficult for transgender men to initiate a relationship than for transgender women[175], but the reasons for this situation are unknown. One could speculate that it is due to differences between transgender men and transgender women and cisgender men and cisgender women: for example, transgender men are generally younger than transgender women at the time of initiating treatment, transgender men are more gynephilic than transgender women are androphilic, and their eventual sexual partners — whether cis or trans — might differ in their own preferences.

Sexual orientation in transgender persons can be fluid and can change during social and medical transition[19,104,117,227,252]. One study has shown that transgender individuals with a sexual orientation towards their assigned sex at birth were more likely to change sexual orientation after transition[117], and reported that, during social and medical transition, transgender men became more androphilic[252].

Sexual satisfaction

Sexual satisfaction is a subjective experience elicited from evaluation of positive and negative feelings associated with one's sexuality and is dependent on an individual's expectations[253]. Sexual satisfaction does not necessarily depend on the level of satisfaction with surgical outcome, as a patient could be discontent with the surgery and still content with sexual life[249] or vice

versa[214]. In the cisgender population, sexual dissatisfaction is common, with ~10–50% of sexually active participants and 20–30% of sexually inactive participants reporting dissatisfaction[159,254].

Sexual satisfaction in transgender women. Between 50% and 100% of transgender women report sexual satisfaction after gender-affirming treatment[193,198,213–216,219,222,225,229,232,236,255]. Studies suggest that sexual satisfaction is similar[256] or worse[162] in transgender women than in cisgender female control participants. Furthermore, gender-affirming treatment improves sexual satisfaction compared with baseline preoperative levels[42,135,175,198,247–249]. Some studies have reported decreased sexual satisfaction after treatment in 5–12.3% of transgender women, possibly related to pain, lack of sensation, or difficulties in relaxing[175,249]. Factors associated with improved or good sexual satisfaction include hormonal treatment[154,257], vaginal function and depth, clitoral sensation, appearance of the vulva and labia minora, natural lubrication[135], satisfaction with vaginoplasty[175], satisfaction with the new genitals[175], being generally satisfied[175], and having a partner[154,175]. Factors associated with low sexual satisfaction include depression[135] and surgical complications such as vaginal stenosis, clitoral necrosis, and postoperative pain in the neovagina or genitals[138].

Sexual satisfaction in transgender men. Sexual satisfaction is reported in 34–100% of transgender men after treatment[118,149,175,214,237,251,258,259]. In studies comparing sexual satisfaction in transgender men with cisgender control participants, the picture is mixed: sexual satisfaction was worse in transgender men than in cisgender heterosexual men[256] but in line with cisgender gay and bisexual men[118]. Similar to transgender women, gender-affirming treatment improves sexual satisfaction in the majority of transgender men[149,175,249,251], but a minority of men report worse sexual satisfaction after treatment, possibly due to prosthesis pain or difficulties in finding a new partner[175]. Increased frequency of sexual activities and orgasm has been associated with better sexual satisfaction in transgender men[259]. One study has also reported a significantly higher sexual satisfaction in transgender men who have undergone metoidioplasty than after phalloplasty[132].

Supporting sexuality in transgender persons

In many aspects transgender persons are just the same as cisgender persons. Sometimes these common aspects are forgotten and assessment and treatment become too transgender specific. To support sexuality in transgender persons, clinicians must apply the same knowledge we have regarding supporting sexuality in cisgender persons and add transgender-medicine-specific knowledge[260].

Sexual history

Sexual dysfunctions are common in both cisgender[261] and transgender persons[37,40,44], a considerable number of whom remain undiagnosed and untreated[261]. Improved training in communication skills related to sexuality, and increased familiarity with dealing with sexual issues can promote improved care of patients who present with sexual issues[53,261,262]. Sexual history taking is a skill[53,261–263], and many clinicians report that sexual history taking is limited by time constraints, fear of offending the patient, discomfort about asking patients sexual questions irrespective of gender, deficits in communications skills, and inadequate training[261,262].

Sexual history and assessment in transgender persons follows the same principles as for history taking in cisgender persons, with the addition of transgender-specific questions. One also needs to be aware of transgender health and to use inclusive language. Sexual history should be part of the medical history and could follow questions about any other aspect of health. Beginning the sexual history with open questions is often helpful, for example, "Are you satisfied with your sexual life?" or "Are there any sexual problems or concerns you would like to discuss?" Relating questions to other patients can also be helpful; for example, "People who have the symptoms you describe or are on this medication also commonly have sexual problems. Is that something you would like to discuss or need help with?"[261,264]. If the patient would like to discuss sexual concerns, follow-up questions should explore the different phases of the sexual response cycle, sexual motivation, sexual desire, arousal, orgasm pain, general sexual satisfaction, and the importance of sexuality for this patient[261,264]. A further assessment should be performed with reference to the biopsychosocial model.

Language can be used to discriminate and marginalize transgender persons and use of transgender-inclusive, non-normative language will facilitate communication regarding transgender general health and sexual health[2,14]. Examples of transgender-inclusive language and questions include consideration of how someone identifies and what pronoun they use, and whether they have a partner or partners (not wife or husband). Sexual orientation is self-defined and transgender persons define their sexual orientation in accordance with their gender identity and not sex assigned at birth[2,14]. Furthermore, sexual history often includes naming of the body parts or body functions related to body dysphoria, which has been shown to actually increase body dysphoria[265]. Thus, use of gender-neutral words, such as "arousal" instead of "erection", and even to ask "What do you call this body part, which in medical language is called the clitoris in cisgender women?"[265].

Many questionnaires and scales are used to assess sexual dysfunction[53,261], but most of them are bigender normative, heteronormative, or require that the patient have a partner[266]. Thus, if questionnaires are used, they should be checked and — if necessary — modified to better meet the needs of transgender patients and not ostracize them[266].

Biological assessment

From a biological perspective, reviewing general health status and, specifically, endocrine status is an important aspect of patient care. Lack of sexual desire in any patient can be caused by hypothyroidism[95,267] or in transgender women by antiandrogen-induced hyperprolactinaemia[268]. Oestrogen and testosterone supplementation in

the transgender patient should be evaluated in order to verify that in-treatment hormone levels are within the target range, which equates to the reference range in healthy cisgender subjects[80]. After surgery, an examination to assess complications that might affect sexual function, such as scar tissue inflammation, rupture of the suture line or additional opening of the posterior commissure in transgender women[269], or urinary fistulae in transgender men[270]. Furthermore, signs of depression as a cause of low sexual desire and/or low self-esteem should be assessed both before and after gender-affirming treatment and treated according to local clinical guidelines. The use of medications with known sexual side effects — such as finasteride, SSRIs, prolactin-raising psychopharmacological agents, and opioids — should be avoided if possible.

The psychosocial sexual assessment

Evaluation of the importance of sexuality to a patient, their sexual satisfaction, and sexual functions, is important to determine how bothersome sexual issues are to a particular person. A psychosocial history, including present and previous mental health problems, should be taken[263]. Important questions include whether the person has been or is in a relationship at present, whether a relationship is important, whether any problems exist in an ongoing relationship, or if they have had difficulties with finding a partner. Furthermore, the clinician should assess whether any relationship difficulties are related to the person's transgender identity, or identified as someone who has transitioned. If the person is gender identified by others according to their gender identity, they should be asked how they feel about telling others about their background. Asking whether the person is comfortable enough to touch, or let others touch, their body, is important and relevant. The clinician should assess the level of residual gender dysphoria that remains, despite ongoing or performed gender-affirming treatment. One could also assess sexual agency and sexual self-esteem. Finally, they should query whether the person is able to live the sexual life that they want, or whether they put up boundaries for themselves, and if they feel safe during sexual encounters or engage in risky sexual behaviour[40,43,271].

Medical treatment of sexual disorders

Testosterone treatment was evaluated in seven transgender women with HSDD with a dose that produces testosterone levels similar to those in cisgender women (300 μg/day) for 24 weeks[272]. Testosterone therapy resulted in a significant improvement in sexual desire (from 2.57 ± 0.53 before treatment to 3.29 ± 0.95 afterwards; $P = 0.025$), as well as in all other domains included in the Brief Profile of Female Sexual Function questionnaire. No unwanted or adverse effects were reported during the study and all but one woman decided to continue treatment after the study was terminated[272]. These data suggest that testosterone therapy could be a treatment option for transgender women suffering from low desire.

Some studies indicate that insufficient hormonal treatment producing subnormal steroid hormone levels (compared with the cisgender reference range) is not uncommon in transgender patients[176,177]. Low levels of serum sex steroids are likely to affect sexual desire[80]. General guidelines concerning choice of hormonal treatment and achieved hormonal levels[80] should be followed, although attention must be paid to the substantial differences observed in individual patients' response and responsiveness. Monitoring hormonal levels once or twice per year (and more often at the beginning of treatment) is essential for assessment of hormone levels and assists in interpretation of clinical responses. Variability exists in uptake, distribution, and elimination of administered oestrogen and testosterone, resulting in considerable interindividual and intraindividual variation. Thus, monitoring must be standardized regarding blood sampling in relation to time of hormone administration, time of day, and fasting or nonfasting conditions. Analytical methods must be accredited and the laboratory involved in a quality-controlled programme ensuring appropriate quality, reproducibility, and sensitivity, and must cover the expected concentration range. Assessment of haemoglobin response and LH suppression are examples of pharmacodynamic end points when assessing androgen treatment. In addition, prolactin levels should be monitored in both transgender men and women. Prolactin is known to mitigate sexual drive and — in cisgender men— erectile function[95]. Prolactin levels can be increased by oestrogen treatment, various central nervous system-targeting drugs (such as antidepressants and anxiolytics) and also gestagens, especially cyproterone acetate[273]. Thus, monitoring of prolactin can be a useful tool to understand potential confounding mechanisms in maintaining acceptable sexual function in trans patients.

PDE5 inhibitors (PDE5i) can be useful in transgender patients. PDE5i cause vasodilatation and increased blood flow, especially in the genitals, via a partly testosterone-dependent mechanism[274]. In the case of erectile dysfunction in transgender women who retain their penis, PDE5i therapy is likely to improve the ability to achieve an erection just as in hypogonadal cisgender men[275]. Intracavernous alprostadil in transgender women has been reported to produce a normal erectile response[122]. Transgender men with a vagina can suffer from dryness due to oestrogen deficit in the vaginal lining, which can be treated with local oestrogen, as in cisgender postmenopausal women[276]. Transgender women with a neovagina sometimes produce vaginal lubrication; if not, lubricants or local oestrogen can be used[277]. Depression and anxiety disorder often hamper sexual function in transgender men and women and are, therefore, important to diagnose and treat. Depression and anxiety disorder can be treated with psychotherapy; if pharmacological treatment is used it is important to avoid drugs with negative sexual side effects.

The role of physical therapy

Physical therapy can be used to reduce pain and tense pelvic muscles in cisgender persons[278,279]. To our knowledge, no studies have specifically investigated the role of physical therapy in transgender individuals, but it is

likely to be helpful for genital pain in transgender people and in cases of narrow neovagina. Furthermore, body awareness therapy can improve sexual health in cisgender women[280] and might, therefore, be useful for transgender persons.

Psychotherapy and psychoeducation

Psychotherapy to address self-esteem, internalized transphobia or transnegativity, depression, and anxiety can be beneficial in trans men and women, and couples therapy can be recommended if relationship issues hamper sexuality[281].

Sexual dysfunctions can be treated with cognitive behavioural therapy, mindfulness-based cognitive therapy and sex therapy, and sensate focus therapy[45,46,282–284]. In transgender women, beneficial effects of sensate focus therapy have been reported but hitherto not published in the peer-reviewed literature[285]. Studies exploring the effect of different psychotherapy techniques to improve sexuality in transgender persons are needed.

In many countries, sex education is part of the school curriculum for teenagers. However, this sex education can be difficult to interpret for transgender teenagers, as it is often cisgender normative. Furthermore, sex education can, in fact, increase gender dysphoria and anxiety. Thus, psychoeducation regarding sexual function in general, as well as social and sexual skills, should be a topic for discussion as part of the counselling offered before and during gender-affirming treatment.

Coping strategies for body dissatisfaction have been published in the literature and made available as self-help material from LGBT organizations[44,98,271]. A useful coping strategy is to conceptualize gendered body parts as acceptable: 'it works, why can't I use it; I enjoy it'; or renaming gender body parts: 'this is my penis', 'I have a frontal opening, not a vagina'. Having sexual encounters with a partner with whom the person feels safe and who respects those parts of the body that are not supposed to be touched can also act as a coping strategy. Dissociation from the body or parts of it, use of sexual fantasies, pleasing others, and not being naked during sexual activity are other possible coping strategies for trans persons to maximize their sexuality and sexual function[44,98,271]. Furthermore, peer-group support is valuable for transgender health in general and is also likely to be valuable for sexual health[286,287].

Conclusions

In general, evidence suggests that medical treatment improves most dimensions of sexual function in transgender men and women who have undergone gender-affirming treatment. Whether this improvement results in a satisfying sexual life is less certain. Research into this topic is subject to numerous methodological disparities and, therefore, results should be interpreted with caution.

Many studies in transgender persons show better results in sexual variables than among cisgender persons, indicating that there might be a tendency to overestimate results, probably due to selection biases. In addition, many transgender persons report that they do not engage in sex at all after gender-affirming treatment[167–170,177,214,237,251]. Historically, transgender persons have been viewed as being hyposexual[21,22,155]. However, this situation is not the case and it raises the question of whether low sexual activity might be a result of insufficient care or the transgender experience itself — all humans need to develop a healthy relationship with their own body during childhood, a process that can be severely hampered by the presence of gender dysphoria. This possibility warrants further investigation.

Most transgender persons request hormone therapy, and it seems that the change in sexuality induced by endocrine therapy is welcomed. The main exception to this positive response to hormone therapy is low sexual desire experienced by some transgender women. However, knowledge is lacking regarding the choice of treatment, the dosing, and the therapeutic goals of endocrine treatment, all of which might result in treatment modalities negatively affecting sexuality.

Surgical intervention is more complex, with transgender persons desiring a variety of interventions from no surgery at all, top-only or bottom-only procedures, to a multitude of operations, making evaluation even more difficult. Among nonoperated transgender women, low sexual desire and erection problems are most common and in those transgender men who have only undergone mastectomy, vaginal dryness is a common clinical problem. The satisfaction with genital surgery is generally high[175], although many patients report pain, arousal, and/or lubrication difficulties after vaginoplasty[163]. Phalloplasty is generally considered satisfactory[132,175,205,237] by patients who have received appropriate advice and counselling[132,288] and have chosen the technique in accordance with their wishes[146]. Satisfaction levels are high in transgender men, despite the fact that erections are not possible without a prosthesis. Pain and other complications are problematic in those with a prosthesis[244]. Metoidioplasty enables a physiological erectile response to sexual stimulation, although it can rarely be used for penetrative sex[150].

In addition to medical aspects of gender-affirming treatment, costs and availability of health care[118], as well as attitudes among health-care providers[29,44,289], can certainly influence transgender persons access to sexual health services.

Regarding research, numbers and quality of studies on transgender persons' sexuality is increasing and several studies have also focused on transgender persons own narratives[43,44,290], which add perspectives that are otherwise difficult to capture. However, methodological improvements are needed, such as the use of appropriate control groups, validated scales, increased sample sizes, and prospective designs. Instruments for assessment should be validated in the transgender population. Furthermore, transgender persons should be asked for their opinions regarding which questions are of importance and on the study design in order to better understand and improve sexual health in individuals with gender dysphoria before and after gender-affirming treatment.

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1. Steensma, T. D., Kreukels, B. P. C., de Vries, A. L. C. & Cohen-Kettenis, P. T. Gender identity development in adolescence. *Hormones Behav.* **64**, 288 (2013).
2. Winter, S. et al. Transgender people: health at the margins of society. *Lancet* **388**, 390–400 (2016).
3. Fraser, L. & Knudson, G. Past and future challenges associated with standards of care for gender transitioning clients. *Psychiatr. Clin. North Am.* **40**, 15–27 (2017).
4. Richards, C. et al. Non-binary or genderqueer genders. *Int. Rev. Psychiatry* **28**, 95–102 (2016).
5. Coleman, E. et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int. J. Transgenderism* **13**, 165–232 (2012).
6. Arcelus, J. & Bouman, W. P. (eds) in *The Transgender Handbook* 1–13 (Nova Science Publishers Inc., 2017).
7. Scheim, A. I. & Bauer, G. R. Sex and gender diversity among transgender persons in Ontario, Canada: results from a respondent-driven sampling survey. *J. Sex. Res.* **52**, 1–14 (2015).
8. Gomez-Gil, E. et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology* **37**, 662–670 (2012).
9. Arcelus, J. et al. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur. Psychiatry* **30**, 807–815 (2015).
10. Collin, L., Reisner, S. L., Tangpricha, V. & Goodman, M. Prevalence of transgender depends on the "case" definition: a systematic review. *J. Sex. Med.* **13**, 613–626 (2016).
11. Wiepjes, C. M. et al. The Amsterdam Cohort of Gender Dysphoria Study: trends in prevalence, treatment, and regrets (1972–2015). *J. Sex. Med.* **15**, 582–590 (2018).
12. Ähs, J. W. et al. Proportion of adults in the general population of Stockholm County who want gender-affirming medical treatment. *PLOS ONE* https://doi.org/10.1371/journal.pone.0204606 (2018).
13. Dhejne, C., Oberg, K., Arver, S. & Landen, M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch. Sexual Behav.* **43**, 1535–1545 (2014).
14. Bouman, W. P. et al. Language and *trans* health. *Int. J. Transgenderism* **18**, 1–6 (2016).
15. Fisk, N. M. Editorial: gender dysphoria syndrome — the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. *West J. Med.* **120**, 386–391 (1974).
16. Cohen-Kettenis, P. T. & Pfafflin, F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch. Sexual Behav.* **39**, 499–513 (2010).
17. Smith, E. S., Junger, J., Derntl, B. & Habel, U. The transsexual brain - a review of findings on the neural basis of transsexualism. *Neurosci. Biobehavioral Rev.* **59**, 251–266 (2015).
18. Nieder, T. O. et al. Age of onset and sexual orientation in transsexual males and females. *J. Sex. Med.* **8**, 783–791 (2011).
19. Nieder, T. O., Elaut, E., Richards, C. & Dekker, A. Sexual orientation of *trans* adults is not linked to outcome of transition-related health care, but worth asking. *Int. Rev. Psychiatry* **28**, 103–111 (2016).
20. Lawrence, A. A. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch. Sexual Behav.* **39**, 514–545 (2010).
21. Person, E. & Ovesey, L. The transsexual syndrome in males. II. Secondary transsexualism. *Am. J. Psychother* **28**, 174–193 (1974).
22. Person, E. & Ovesey, L. The transsexual syndrome in males. I. Primary transsexualism. *Am. J. Psychother* **28**, 4–20 (1974).
23. Benjamin, H. *The Transsexual Phenomenon: a Scientific Report on Transsexualism and Sex Conversion in the Human Male and Female* (The Julian Press Inc., NY, 1966).
24. Pimenoff, V. & Pfäfflin, F. Transsexualism: treatment outcome of compliant and noncompliant patients. *Int. J. Transgenderism* **13**, 37–44 (2011).
25. Walworth, J. R. in *Gender Blending* (eds Bullough, B., Bullough, V. L. & Elias, J.) 352–369 (Prometheus Books, 1997).
26. The International Lesbian, Gay, Bisexual, Trans and Intersex Association. *Annual review of the human rights situation of lesbian, gay, bisexual, trans and intersex people in Europe* (ILGA, 2017).
27. Human Rights Watch. *World report* (Human Rights Watch, 2017).
28. The International Lesbian, Gay, Bisexual, Trans and Intersex Association. *Sexual orientation laws in the world - overview* (ILGA, 2017).
29. Zeluf, G. et al. Health, disability and quality of life among *trans* people in Sweden-a web-based survey. *BMC Publ. Health* **16**, 903 (2016).
30. European Union Agency for Fundamental Rights. *Being trans in the EU - comparative analysis of the EU LGBT survey data* (FRA, 2014).
31. World Health Organization. *Sexual health, human rights and the law* (WHO, 2015).
32. McCabe, M. P. et al. Definitions of sexual dysfunctions in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J. Sex. Med.* **13**, 135–143 (2016).
33. Basson, R. et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J. Urol.* **163**, 888–893 (2000).
34. Bitzer, J., Giraldi, A. & Pfaus, J. Sexual desire and hypoactive sexual desire disorder in women. Introduction and overview. Standard operating procedure (SOP Part 1). *J. Sex. Med.* **10**, 36–49 (2013).
35. Dundon, C. M. & Rellini, A. H. More than sexual function: predictors of sexual satisfaction in a sample of women age 40–70. *J. Sex. Med.* **7**, 896–904 (2010).
36. McClelland, S. I. Intimate justice: a critical analysis of sexual satisfaction. *Soc. Personal Psychol. Compass* **4**, 663–680 (2010).
37. Klein, G. J. & Gorzalka, B. B. Sexual functioning in transsexuals following hormone therapy and genital surgery: a review. *J. Sex. Med.* **6**, 2922–2939 (2009).
38. Pfaus, J. G. Pathways of sexual desire. *J. Sex. Med.* **6**, 1506–1533 (2009).
39. Pujols, Y., Seal, B. N. & Meston, C. M. The association between sexual satisfaction and body image in women. *J. Sex. Med.* **7**, 905–916 (2010).
40. Nikkelen, S. W. C. & Kreukels, B. P. C. Sexual experiences in transgender people: the role of desire for gender-confirming interventions, psychological well-being, and body satisfaction. *J. Sex Marital Ther.* **44**, 370–381 (2018).
41. Shepler, D. K., Smendik, J. M., Cusick, K. M. & Tucker, D. R. Predictors of sexual satisfaction for partnered lesbian, gay, and bisexual adults. Psychol. Sexual Orient. *Gender Divers.* **5**, 25–35 (2018).
42. Murad, M. H. et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin. Endocrinol. (Oxf)* **72**, 214–231 (2010).
43. Doorduin, T. & van Berlo, W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J. Homosex.* **61**, 654–672 (2014).
44. Lindroth, M., Zeluf, G., Mannheimer, L. N. & Deogan, C. Sexual health among transgender people in Sweden. *Int. J. Transgend.* **18**, 318–327 (2018).
45. Masters, W. H. & Johnson, V. E. *Human Sexual Inadequacy* (Little Brown and Co., Boston, 1970).
46. Kaplan, H. S. *New Sex Therapy: Active Treatment of Sexual Dysfunctions* (Routledge, 2013).
47. Bancroft, J. & Janssen, E. The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunction. *Neurosci. Biobehavioral Rev.* **24**, 571–579 (2000).
48. Perelman, M. A. A new combination treatment for premature ejaculation: a sex therapist's perspective. *J. Sex. Med.* **3**, 1004–1012 (2006).
49. Toates, F. An integrative theoretical framework for understanding sexual motivation, arousal, and behavior. *J. Sex. Res.* **46**, 168–193 (2009).
50. Basson, R. Human sex-response cycles. *J. Sex. Marital Ther.* **27**, 33–43 (2001).
51. Brom, M., Both, S., Laan, E., Everaerd, W. & Spinhoven, P. The role of conditioning, learning and dopamine in sexual behavior: a narrative review of animal and human studies. *Neurosci. Biobehavioral Rev.* **38**, 38–59 (2014).
52. Brom, M. et al. The influence of emotion down-regulation on the expectation of sexual reward. *Behav. Ther.* **46**, 379–394 (2015).
53. Hatzichristou, D. et al. Diagnosing sexual dysfunction in men and women: sexual history taking and the role of symptom scales and questionnaires. *J. Sex. Med.* **13**, 1166–1182 (2016).
54. Raheem, O. A., Su, J. J., Wilson, J. R. & Hsieh, T. C. The association of erectile dysfunction and cardiovascular disease: a systematic critical review. *Am. J. Mens Health* **11**, 552–563 (2017).
55. Lew-Starowicz, M. & Gianotten, W. L. Sexual dysfunction in patients with multiple sclerosis. *Handb. Clin. Neurol.* **130**, 357–370 (2015).
56. Clayton, A. H., Croft, H. A. & Handiwala, L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgraduate Med.* **126**, 91–99 (2014).
57. Ali, K., Raphael, J., Khan, S., Labib, M. & Duarte, R. The effects of opioids on the endocrine system: an overview. *Postgrad. Med. J.* **92**, 677–681 (2016).
58. Brennan, M. J. The effect of opioid therapy on endocrine function. *Am. J. Med.* **126**, S12–S18 (2013).
59. Bhasin, S., Enzlin, P., Coviello, A. & Basson, R. Sexual dysfunction in men and women with endocrine disorders. *Lancet* **369**, 597–611 (2007).
60. Lewis, R. W. et al. Definitions/epidemiology/risk factors for sexual dysfunction. *J. Sex. Med.* **7**, 1598–1607 (2010).
61. Haney, N. M., Alzweri, L. M. & Hellstrom, W. J. G. Male orgasmic dysfunction post-radical pelvic surgery. *Sex. Med. Rev.* **6**, 429–451 (2018).
62. Haefner, H. K. et al. The impact of vulvar lichen sclerosus on sexual dysfunction. *J. Women' Health* **23**, 765–770 (2014).
63. Rantell, A., Apostolidis, A., Anding, R., Kirschner-Hermanns, R. & Cardozo, L. How does lower urinary tract dysfunction affect sexual function in men and women? ICI-RS 2015-part 1. *Neurourol. Urodyn.* **36**, 949–952 (2017).
64. Clayton, A. H. Sexual function and dysfunction in women. *Psychiatr. Clin. North Am.* **26**, 673–682 (2003).
65. Cash, T. F. & Fleming, E. C. The impact of body image experiences: development of the body image quality of life inventory. *Int. J. Eat Disord.* **31**, 455–460 (2002).
66. Simon, W. & Gagnon, J. Sexual scripts: permanence and change. *Arch. Sex. Behav.* **15**, 97–120 (1986).
67. Timmermans, E. & Van den Bulck, J. Casual sexual scripts on the screen: a quantitative content analysis. *Arch. Sex. Behav.* **47**, 1481–1496 (2018).
68. Pomeroy, W. B. in *Transsexualism and Sex Reassignment* (eds Green, G. & Money, J.) 183–188 (Johns Hopkins Univ. Press,1969).
69. Serano, J. Psychology, sexualization and trans-invalidations. *8th Ann. Philadelphia Trans-Health Conf.* http://www.juliaserano.com/av/Serano-TransInvalidations.pdf (2009).
70. Giraldi, A., Rellini, A. H., Pfaus, J. & Laan, E. Female sexual arousal disorders. *J. Sex. Med.* **10**, 58–73 (2013).
71. Almeida, M. et al. Estrogens and androgens in skeletal physiology and pathophysiology. *Physiol. Rev.* **97**, 135–187 (2017).
72. McEwen, B. S. & Milner, T. A. Understanding the broad influence of sex hormones and sex differences in the brain. *J. Neurosci. Res.* **95**, 24–39 (2017).
73. Sansone, A., Romanelli, F., Sansone, M., Lenzi, A. & Di Luigi, L. Gynecomastia and hormones. *Endocr* **55**, 46–53 (2017).
74. Randall, V. A. in *Hair Growth and Disorders* (eds Blume-Peytavi, U., Tosti, A. & Trüeb, R. M.) 23–39 (Springer, 2008).
75. Vita, R., Settineri, S., Liotta, M., Benvenga, S. & Trimarchi, F. Changes in hormonal and metabolic parameters in transgender subjects on cross-sex hormone therapy: a cohort study. *Maturitas* **107**, 92–96 (2018).
76. Sinnecker, G. & Köhler, S. Sex hormone binding globulin response to the anabolic steroid stanozolol. Preliminary evidence for it's suitability as a biological androgen sensitivity test. *Pediatr. Res.* **23**, 131 (1988).
77. Grisendi, V. et al. Age-specific reference values for serum FSH and estradiol levels throughout the reproductive period. *Gynecol. Endocrinol.* **30**, 451–455 (2014).
78. Jasuja, G. K. et al. Age trends in estradiol and estrone levels measured using liquid chromatography tandem mass spectrometry in community-dwelling men of the Framingham Heart Study. *J. Gerontol. A Biol. Sci. Med. Sci.* **68**, 733–740 (2013).
79. Finkelstein, J. S. et al. Gonadal steroids and body composition, strength, and sexual function in men. *N. Engl. J. Med.* **369**, 1011–1022 (2013).
80. Hembree, W. C. et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society* clinical practice guideline. *J. Clin. Endocrinol. Metab.* **102**, 3869–3903 (2017).
81. Reisner, S. L. et al. Global health burden and needs of transgender populations: a review. *Lancet* **388**, 412–436 (2016).
82. Frisen, L. et al. Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to CYP21A2 deficiency. *J. Clin. Endocrinol. Metab.* **94**, 3432–3439 (2009).

83. Kreukels, B. P. C. et al. Gender dysphoria and gender change in disorders of sex development/intersex conditions: results from the dsd-LIFE Study. *J. Sex. Med.* **15**, 777–785 (2018).
84. Basson, R. Testosterone therapy for reduced libido in women. *Ther. Adv. Endocrinol. Metab.* **1**, 155–164 (2010).
85. Corona, G. et al. Testosterone supplementation and sexual function: a meta-analysis study. *J. Sex. Med.* **11**, 1577–1592 (2014).
86. Arver, S. et al. Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. *J. Urol.* **155**, 1604–1608 (1996).
87. Bancroft, J. The endocrinology of sexual arousal. *J. Endocrinol.* **186**, 411–427 (2005).
88. Fooladi, E. et al. Testosterone improves antidepressant-emergent loss of libido in women: findings from a randomized, double-blind, placebo-controlled trial. *J. Sex. Med.* **11**, 831–839 (2014).
89. Achilli, C. et al. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil. Steril.* **107**, 475–482 (2017).
90. Davis, S. R. & Braunstein, G. D. Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *J. Sex. Med.* **9**, 1134–1148 (2012).
91. Sherwin, B. B., Gelfand, M. M. & Brender, W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom. Med.* **47**, 339–351 (1985).
92. Dennerstein, L., Burrows, G. D., Wood, C. & Hyman, G. Hormones and sexuality: effect of estrogen and progestogen. *Obstetr. Gynecol.* **56**, 316–322 (1980).
93. Buster, J. E. et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstetr. Gynecol.* **105**, 944–952 (2005).
94. Davis, S. R. et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* **13**, 387–396 (2006).
95. Corona, G., Isidori, A. M., Aversa, A., Burnett, A. L. & Maggi, M. Endocrinologic control of men's sexual desire and arousal/erection. *J. Sex. Med.* **13**, 317–337 (2016).
96. Levin, R. J. The pharmacology of the human female orgasm - its biological and physiological backgrounds. *Pharmacol. Biochem. Behav.* **121**, 62–70 (2014).
97. van de Grift, T. C. et al. Effects of medical interventions on gender dysphoria and body image: a follow-up study. *Psychosom. Med.* **79**, 815–823 (2017).
98. Bettcher, T. M. When selves have sex: what the phenomenology of *trans* sexuality can teach about sexual orientation. *J. Homosex.* **61**, 605–620 (2014).
99. van de Grift, T. C. et al. Body satisfaction and physical appearance in gender dysphoria. *Arch. Sexual Behav.* **45**, 575–585 (2016).
100. Fleming, M. Z., MacGowan, B. R., Robinson, L., Spitz, J. & Salt, P. The body image of the postoperative female-to-male transsexual. *J. Consult. Clin. Psychol.* **50**, 461–462 (1982).
101. Lindgren, T. W. & Pauly, I. B. A body image scale for evaluating transsexuals. *Arch. Sexual Behav.* **4**, 639–656 (1975).
102. Weigert, R., Frison, E., Sessiecq, Q., Al Mutairi, K. & Casoli, V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast. Reconstr. Surg.* **132**, 1421–1429 (2013).
103. Veale, J. F., Lomax, T. & Clarke, D. Identity-defense model of gender-variant development. *Int. J. Transgenderism* **12**, 125–138 (2010).
104. Cerwenka, S. et al. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J. Sex. Marital Ther.* **40**, 457–471 (2014).
105. Bandini, E. et al. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int. J. Impot. Res.* **23**, 276–285 (2011).
106. Prunas, A. et al. Experiences of discrimination, harassment, and violence in a sample of Italian transsexuals who have undergone sex-reassignment surgery. *J. Interpers. Violence* **33**, 2225–2240 (2016).
107. Gehring, D. & Knudson, G. Prevalence of childhood trauma in a clinical population of transsexual people. *Int. J. Transgenderism* **8**, 23–30 (2005).
108. Devor, H. Transsexualism, dissociation, and child abuse: an initial discussion based on nonclinical data. *J. Psychol. Hum. Sexual.* **6**, 49–72 (1994).
109. Zucker, K. J. & Kuksis, M. Gender dysphoria and sexual abuse: a case report. *Child Abuse Negl.* **14**, 281–283 (1990).
110. Andersen, J. P. & Blosnich, J. Disparities in adverse childhood experiences among sexual minority and heterosexual adults: results from a multi-state probability-based sample. *PLOS ONE* **8**, e54691 (2013).
111. Corliss, H. L., Cochran, S. D. & Mays, V. M. Reports of parental maltreatment during childhood in a United States population-based survey of homosexual, bisexual, and heterosexual adults. *Child Abuse Negl.* **26**, 1165–1178 (2002).
112. Simon, L., Zsolt, U., Fogd, D. & Czobor, P. Dysfunctional core beliefs, perceived parenting behavior and psychopathology in gender identity disorder: a comparison of male-to-female, female-to-male transsexual and nontranssexual control subjects. *J. Behav. Ther. Exp. Psychiatry* **42**, 38–45 (2011).
113. Chen, L. P. et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. *Mayo Clin. Proc.* **85**, 618–629 (2010).
114. Bjorkenstam, E., Burstrom, B., Vinnerljung, B. & Kosidou, K. Childhood adversity and psychiatric disorder in young adulthood: an analysis of 107,704 Swedes. *J. Psychiatr. Res.* **77**, 67–75 (2016).
115. Laumann, E. O., Gagnon, J. H., Michael, R. T. & Michaels, S. *The Social Organization of Sexuality: Sexual practices in the United States.* (Univ. of Chicago Press, 1994).
116. Van Houdenhove, E., Gijs, L., T'Sjoen, G. & Enzlin, P. Asexuality: a multidimensional approach. *J. Sex. Res.* **52**, 669–678 (2015).
117. Auer, M. K., Fuss, J., Hohne, N., Stalla, G. K. & Sievers, C. Transgender transitioning and change of self-reported sexual orientation. *PLOS ONE* **9**, e110016 (2014).
118. Bockting, W., Benner, A. & Coleman, E. Gay and bisexual identity development among female-to-male transsexuals in North America: emergence of a transgender sexuality. *Arch. Sexual Behav.* **38**, 688–701 (2009).
119. Cerwenka, S. et al. Intimate partnerships and sexual health in gender-dysphoric individuals before the start of medical treatment. *Int. J. Sexual Health* **26**, 52–65 (2014).
120. Alegria, C. A. Relationship challenges and relationship maintenance activities following disclosure of transsexualism. *J. Psychiatr. Mental Health Nurs.* **17**, 909–916 (2010).
121. Nieschlag, E. in *Fertility Control — Handbook of Experimental Pharmacology* Vol. 198 (eds Habenicht, U. F. & Aitken, R.) 197–223 (Springer, Berlin, 2010).
122. Bettocchi, C. et al. The effects of androgen depletion on human erectile function: a prospective study in male-to-female transsexuals. *Int. J. Impot. Res.* **16**, 544–546 (2004).
123. Costa, R., Carmichael, P. & Colizzi, M. To treat or not to treat: puberty suppression in childhood-onset gender dysphoria. *Nat. Rev. Urol.* **13**, 456–462 (2016).
124. Sorge, R. E. & Totsch, S. K. Sex differences in Pain. *J. Neurosci. Res.* **95**, 1271–1281 (2017).
125. Aloisi, A. M., Ceccarelli, I., Fiorenzani, P., De Padova, A. M. & Massafra, C. Testosterone affects formalin-induced responses differently in male and female rats. *Neurosci. Lett.* **361**, 262–264 (2004).
126. Ceccarelli, I., Scaramuzzino, A., Massafra, C. & Aloisi, A. M. The behavioral and neuronal effects induced by repetitive nociceptive stimulation are affected by gonadal hormones in male rats. *Pain* **104**, 35–47 (2003).
127. Hau, M., Dominguez, O. A. & Evrard, H. C. Testosterone reduces responsiveness to nociceptive stimuli in a wild bird. *Horm. Behav.* **46**, 165–170 (2004).
128. Ji, Y., Hu, B., Li, J. & Traub, R. J. Opposing roles of estradiol and testosterone on stress-induced visceral hypersensitivity in rats. *J. Pain* **19**, 764–776 (2018).
129. Schertzinger, M., Wesson-Sides, K., Parkitny, L. & Younger, J. Daily fluctuations of progesterone and testosterone are associated with fibromyalgia pain severity. *J. Pain* **19**, 410–417 (2017).
130. White, H. D. et al. Treatment of pain in fibromyalgia patients with testosterone gel: pharmacokinetics and clinical response. *Int. Immunopharmacol.* **27**, 249–256 (2015).
131. Aloisi, A. M. et al. Cross-sex hormone administration changes pain in transsexual women and men. *Pain* **132** (Suppl. 1), 60–67 (2007).
132. van de Grift, T. C. et al. A longitudinal study of motivations before and psychosexual outcomes after genital gender-confirming surgery in transmen. *J. Sex. Med.* **14**, 1621–1628 (2017).
133. Morrison, S. D. et al. Long-term outcomes of rectosigmoid neocolporrhaphy in male-to-female gender reassignment surgery. *Plast. Reconstructive Surg.* **136**, 386–394 (2015).
134. Selvaggi, G. & Bellringer, J. Gender reassignment surgery: an overview. *Nat. Rev. Urol.* **8**, 274–282 (2011).
135. LeBreton, M. et al. Genital sensory detection thresholds and patient satisfaction with vaginoplasty in male-to-female transgender women. *J. Sex. Med.* **14**, 274–281 (2017).
136. Selvaggi, G. et al. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann. Plast. Surg.* **58**, 427–433 (2007).
137. Sigurjonsson, H., Mollermark, C., Rinder, J., Farnebo, F. & Lundgren, T. K. Long-term sensitivity and patient-reported functionality of the neoclitoris after gender reassignment surgery. *J. Sex. Med.* **14**, 269–275 (2017).
138. Lawrence, A. A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch. Sexual Behav.* **35**, 717–727 (2006).
139. Morrison, S. D., Chen, M. L. & Crane, C. N. An overview of female-to-male gender-confirming surgery. *Nat. Rev. Urol.* **14**, 486–500 (2017).
140. Ascha, M., Massie, J. P., Morrison, S. D., Crane, C. N. & Chen, M. L. Outcomes of single stage phalloplasty by pedicled anterolateral thigh flap versus radial forearm free flap in gender confirming surgery. *J. Urol.* **199**, 206–214 (2018).
141. Neuville, P. et al. Surgical outcomes of erectile implants after phalloplasty: retrospective analysis of 95 procedures. *J. Sex. Med.* **13**, 1758–1764 (2016).
142. Kim, S. et al. The anatomy of forearm free flap phalloplasty for transgender surgery. *Clin. Anat.* **31**, 145–151 (2018).
143. Kim, S. et al. The anatomy of abdominal flap phalloplasty for transgender surgery. *Clin. Anat.* **31**, 181–186 (2018).
144. Terrell, M. et al. Anatomy of the pedicled anterolateral thigh flap for phalloplasty in transitioning males. *Clin. Anat.* **31**, 160–168 (2018).
145. Fang, R. H., Kao, Y. S., Ma, S. & Lin, J. T. Phalloplasty in female-to-male transsexuals using free radial osteocutaneous flap: a series of 22 cases. *Br. J. Plast. Surg.* **52**, 217–222 (1999).
146. Jacobsson, J., Andreasson, M., Kolby, L., Elander, A. & Selvaggi, G. Patients' priorities regarding female-to-male gender affirmation surgery of the genitalia-a pilot study of 47 patients in Sweden. *J. Sex. Med.* **14**, 857–864 (2017).
147. Hage, J. J., Bout, C. A., Bloem, J. J. & Megens, J. A. Phalloplasty in female-to-male transsexuals: what do our patients ask for? *Ann. Plast. Surg.* **30**, 323–326 (1993).
148. Remington, A. C. et al. Outcomes after phalloplasty: do transgender patients and multiple urethral procedures carry a higher rate of complication? *Plast. Reconstr. Surg.* **141**, 220e–229e (2018).
149. Vukadinovic, V., Stojanovic, B., Majstorovic, M. & Milosevic, A. The role of clitoral anatomy in female to male sex reassignment surgery. *TheScientificWorld-Journal* **2014**, 437378 (2014).
150. Hage, J. J. & van Turnhout, A. A. Long-term outcome of metaidoioplasty in 70 female-to-male transsexuals. *Ann. Plast. Surg.* **57**, 312–316 (2006).
151. Takamatsu, A. & Harashina, T. Labial ring flap: a new flap for metaidoioplasty in female-to-male transsexuals. *J. Plast. Reconstr Aesthet. Surg.* **62**, 318–325 (2009).
152. Olson-Kennedy, J., Warus, J., Okonta, V., Belzer, M. & Clark, L. F. Chest reconstruction and chest dysphoria in transmasculine minors and young adults: comparisons of nonsurgical and postsurgical cohorts. *JAMA Pediatr.* **172**, 431–436 (2018).
153. van de Grift, T. C. et al. Body image in transmen: multidimensional measurement and the effects of mastectomy. *J. Sex. Med.* **13**, 1778–1786 (2016).
154. Bartolucci, C. et al. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J. Sex. Med.* **12**, 180–188 (2015).
155. Wålinder, J. *Transsexualism: a Study of Forty-Three Cases* (Akademiförlaget/Gumpert, 1967).
156. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Association, 2013).
157. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Tenth Revision* (WHO, 1992).
158. Martin, S. A. et al. Predictors of sexual dysfunction incidence and remission in men. *J. Sex. Med.* **11**, 1136–1147 (2014).

159. Mitchell, K. R. et al. Sexual function in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet* **382**, 1817–1829 (2013).
160. Wierckx, K. et al. Sexual desire in *trans* persons: associations with sex reassignment treatment. *J. Sex. Med.* **11**, 107–118 (2014).
161. Wierckx, K. et al. Cross-sex hormone therapy in *trans* persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J. Sex. Med.* **11**, 1999–2011 (2014).
162. Elaut, E. et al. Hypoactive sexual desire in transsexual women: prevalence and association with testosterone levels. *Eur. J. Endocrinol.* **158**, 393–399 (2008).
163. Weyers, S. et al. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J. Sex. Med.* **6**, 752–760 (2009).
164. Rosen, R. C. et al. Correlates of sexually related personal distress in women with low sexual desire. *J. Sex. Med.* **6**, 1549–1560 (2009).
165. Leiblum, S. R., Koochaki, P. E., Rodenberg, C. A., Barton, I. P. & Rosen, R. C. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* **13**, 46–56 (2006).
166. Laumann, E. O. et al. Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int. J. Impot. Res.* **17**, 39–57 (2005).
167. Bouman, M. B. et al. Patient-reported esthetic and functional outcomes of primary total laparoscopic intestinal vaginoplasty in transgender women with penoscrotal hypoplasia. *J. Sex. Med.* **13**, 1438–1444 (2016).
168. Buncamper, M. E. et al. Aesthetic and functional outcomes of neovaginoplasty using penile skin in male-to-female transsexuals. *J. Sex. Med.* **12**, 1626–1634 (2015).
169. Reed, H. M., Yanes, R. E., Delto, J. C., Omarzai, Y. & Imperatore, K. Non-grafted vaginal depth augmentation for transgender atresia, our experience and survey of related procedures. *Aesthet. Plast. Surg.* **39**, 733–744 (2015).
170. van der Sluis, W. B. et al. Long-term follow-up of transgender women after secondary intestinal vaginoplasty. *J. Sex. Med.* **13**, 702–710 (2016).
171. Manrique, O. J. et al. Gender-confirmation surgery using the pedicle transverse colon flap for vaginal reconstruction: a clinical outcome and sexual function evaluation study. *Plast. Reconstr. Surg.* **141**, 767–771 (2018).
172. Buncamper, M. E. et al. Penile inversion vaginoplasty with or without additional full-thickness skin graft: to graft or not to graft? *Plast. Reconstr. Surg.* **139**, 649e–656e (2017).
173. ter Kuile, M. M., Brauer, M. & Laan, E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. *J. Sex. Marital Ther.* **32**, 289–304 (2006).
174. Rosen, R. et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J. Sex. Marital Ther.* **26**, 191–208 (2000).
175. De Cuypere, G. et al. Sexual and physical health after sex reassignment surgery. *Arch. Sexual Behav.* **34**, 679–690 (2005).
176. Costantino, A. et al. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J. Sex. Marital Ther.* **39**, 321–335 (2013).
177. Wierckx, K. et al. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur. J. Endocrinol.* **165**, 331–337 (2011).
178. Rowniak, S., Chesla, C., Rose, C. D. & Holzemer, W. L. Transmen: the HIV risk of gay identity. *AIDS Educ.* **23**, 508–520 (2011).
179. Coleman, E. Is your patient suffering from compulsive sexual behavior? *Psychiatr. Ann.* **22**, 320–325 (1992).
180. Kuzma, J. M. & Black, D. W. Epidemiology, prevalence, and natural history of compulsive sexual behavior. *Psychiatr. Clin. North Amer.* **31**, 603–611 (2008).
181. Odlaug, B. L. et al. Compulsive sexual behavior in young adults. 25, 193–200 (2013).
182. Pastor, Z. & Chmel, R. Differential diagnostics of female "sexual" fluids: a narrative review. *Int. Urogynecol. J.* **29**, 621–629 (2018).
183. Geer, J. H., Morokoff, P. & Greenwood, P. Sexual arousal in women: the development of a measurement device for vaginal blood volume. *Arch. Sexual Behav.* **3**, 559–564 (1974).
184. Bouchard, K. N., Chivers, M. L. & Pukall, C. F. Effects of genital response measurement device and stimulus characteristics on sexual concordance in women. *J. Sex. Res.* **54**, 1197–1208 (2017).
185. Oh, S. K. et al. Brain activation in response to visually evoked sexual arousal in male-to-female transsexuals: 3.0 tesla functional magnetic resonance imaging. *Kor. J. Radiol.* **13**, 257–264 (2012).
186. Kim, G. W. & Jeong, G. W. Neural mechanisms underlying sexual arousal in connection with sexual hormone levels: a comparative study of the postoperative male-to-female transsexuals and premenopausal and menopausal women. *Neuroreport* **25**, 693–700 (2014).
187. Arnow, B. A. et al. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. *Neuroscience* **158**, 484–502 (2009).
188. Laan, E., Everaerd, W., van der Velde, J. & Geer, J. H. Determinants of subjective experience of sexual arousal in women: feedback from genital arousal and erotic stimulus content. *Psychophysiology* **32**, 444–451 (1995).
189. Hage, J. J. & Karim, R. B. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast. Reconstr. Surg.* **105**, 1222–1227 (2000).
190. Saleh, A., Abboudi, H., Ghazal-Aswad, M., Mayer, E. K. & Vale, J. A. Management of erectile dysfunction post-radical prostatectomy. *Res. Rep. Urol.* **7**, 19–33 (2015).
191. Isidori, A. M. et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. *Eur. Urol.* **65**, 99–112 (2014).
192. Brotto, L. A. et al. Psychophysiological and subjective sexual arousal to visual sexual stimuli in new women. *J. Psychosomat. Obstetr. Gynecol.* **26**, 237–244 (2009).
193. Schroder, M. & Carroll, R. A. New women: sexological outcomes of male-to-female gender reassignment surgery. *J. Sex. Educ. Ther.* **24**, 137–146 (1999).
194. Lawrence, A. A., Latty, E. M., Chivers, M. L. & Bailey, J. M. Measurement of sexual arousal in postoperative male-to-female transsexuals using vaginal photoplethysmography. *Arch. Sexual Behav.* **34**, 135–145 (2005).
195. Colebunders, B., Brondeel, S., D'Arpa, S., Hoebeke, P. & Monstrey, S. An update on the surgical treatment for transgender patients. *Sex. Med. Rev.* **5**, 103–109 (2017).
196. Kwun Kim, S. et al. Long-term results in patients after rectosigmoid vaginoplasty. *Plast. Reconstr. Surg.* **112**, 143–151 (2003).
197. Hage, J. J., Karim, R. B., Asscheman, H., Bloemena, E. & Cuesta, M. A. Unfavorable long-term results of rectosigmoid neocolpopoiesis. *Plast. Reconstr. Surg.* **95**, 842–848; discussion 849–850 (1995).
198. Imbimbo, C. et al. A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. *J. Sex. Med.* **6**, 2736–2745 (2009).
199. Schilt, K. & Windsor, E. The sexual habitus of transgender men: negotiating sexuality through gender. *J. Homosex.* **61**, 732–748 (2014).
200. Baldassarre, M. et al. Effects of long-term high dose testosterone administration on vaginal epithelium structure and estrogen receptor-alpha and -beta expression of young women. *Int. J. Impot. Res.* **25**, 172–177 (2013).
201. Kingsberg, S. A., Wysocki, S., Magnus, L. & Krychman, M. L. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. *J. Sex. Med.* **10**, 1790–1799 (2013).
202. Kokcu, A. et al. Does surgical menopause affect sexual performance differently from natural menopause? *J. Sex. Med.* **12**, 1407–1414 (2015).
203. Garaffa, G., Christopher, N. A. & Ralph, D. J. Total phallic reconstruction in female-to-male transsexuals. *Eur. Urol.* **57**, 715–722 (2010).
204. Kim, S. K., Lee, K. C., Kwon, Y. S. & Cha, B. H. Phalloplasty using radial forearm osteocutaneous free flaps in female-to-male transsexuals. *J. Plast. Reconstr Aesthet Surg.* **62**, 309–317 (2009).
205. Garcia, M. M., Christopher, N. A., De Luca, F., Spilotros, M. & Ralph, D. J. Overall satisfaction, sexual function and the durability of neophallus dimensions following staged female to male genital gender confirming surgery: the Institute of Urology, London, U. K. experience. *Transl Androl. Urol.* **3**, 156–162 (2014).
206. Leriche, A. et al. Long-term outcome of forearm flee-flap phalloplasty in the treatment of transsexualism. *BJU Int.* **101**, 1297–1300 (2008).
207. Djordjevic, M. L. et al. Metoidioplasty as a single stage sex reassignment surgery in female transsexuals: Belgrade experience. *J. Sex. Med.* **6**, 1306–1313 (2009).
208. Cohanzad, S. Extensive metoidioplasty as a technique capable of creating a compatible analogue to a natural penis in female transsexuals. *Aesthet. Plast. Surg.* **40**, 130–138 (2016).
209. Taylor, J. F., Rosen, R. C. & Leiblum, S. R. Self-report assessment of female sexual function: psychometric evaluation of the brief index of sexual functioning for women. *Arch. Sexual Behav.* **23**, 627–643 (1994).
210. Wise, N. J., Frangos, E. & Komisaruk, B. R. Brain activity unique to orgasm in women: an fMRI analysis. *J. Sex. Med.* **14**, 1380–1391 (2017).
211. Georgiadis, J. R. et al. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. *Eur. J. Neurosci.* **24**, 3305–3316 (2006).
212. van Netten, J. J., Georgiadis, J. R., Nieuwenburg, A. & Kortekaas, R. 8–13 hz fluctuations in rectal pressure are an objective marker of clitorally-induced orgasm in women. *Arch. Sexual Behav.* **37**, 279–285 (2008).
213. Eldh, J. Construction of a neovagina with preservation of the glans penis as a clitoris in male transsexuals. *Plast. Reconstr. Surg.* **91**, 895–900; discussion 901–903 (1993).
214. Eldh, J., Berg, A. & Gustafsson, M. Long-term follow up after sex reassignment surgery. *Scand. J. Plast. Reconstr. Surg. Hand Surg.* **31**, 39–45 (1997).
215. Rehman, J., Lazer, S., Benet, A. E., Schaefer, L. C. & Melman, A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch. Sexual Behav.* **28**, 71–89 (1999).
216. Rehman, J. & Melman, A. Formation of neoclitoris from glans penis by reduction glansplasty with preservation of neurovascular bundle in male-to-female gender surgery: functional and cosmetic outcome. *J. Urol.* **161**, 200–206 (1999).
217. Hage, J. J. & Karim, R. B. Sensate pedicled neoclitoroplasty for male transsexuals: Amsterdam experience in the first 60 patients. *Ann. Plast. Surg.* **36**, 621–624 (1996).
218. Rubin, S. O. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J. Urol. Nephrol. Suppl.* **154**, 1–28 (1993).
219. Hess, J., Neto, R. R., Panic, L., Rübben, H. & Senf, W. Satisfaction with male-to-female gender reassignment surgery: results of a retrospective analysis. *Dtsch. Arztebl. Int.* **111**, 795–801 (2014).
220. Bentler, P. M. A typology of transsexualism: gender identity theory and data. *Arch. Sexual Behav.* **5**, 567–584 (1976).
221. Krege, S., Bex, A., Lummen, G. & Rubben, H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int.* **88**, 396–402 (2001).
222. Amend, B., Seibold, J., Toomey, P., Stenzl, A. & Sievert, K. D. Surgical reconstruction for male-to-female sex reassignment. *Eur. Urol.* **64**, 141–149 (2013).
223. Rakic, Z., Starcevic, V., Maric, J. & Kelin, K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch. Sexual Behav.* **25**, 515–525 (1996).
224. Giraldo, F. et al. Corona glans clitoroplasty and urethropreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. *Plast. Reconstr. Surg.* **114**, 1543–1550 (2004).
225. Freundt, I., Toolenaar, T. A., Huikeshoven, F. J., Jeekel, H. & Drogendijk, A. C. Long-term psychosexual and psychosocial performance of patients with a sigmoid neovagina. *Am. J. Obstetr. Gynecol.* **169**, 1210–1214 (1993).
226. Zavlin, D. et al. Male-to-female sex reassignment surgery using the combined vaginoplasty technique: satisfaction of transgender patients with aesthetic, functional, and sexual outcomes. *Aesthet. Plast. Surg.* **42**, 178–187 (2018).
227. Lawrence, A. A. Sexuality before and after male-to-female sex reassignment surgery. *Arch. Sexual Behav.* **34**, 147–166 (2005).
228. Lindemalm, G., Korlin, D. & Uddenberg, N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch. Sexual Behav.* **15**, 187–210 (1986).

229. Goddard, J. C. et al. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int.* **100**, 607–613 (2007).
230. Soli, M. et al. Male to female gender reassignment: modified surgical technique for creating the neoclitoris and mons veneris. *J. Sex. Med.* **5**, 210–216 (2008).
231. Lief, H. I. & Hubschman, L. Orgasm in the postoperative transsexual. *Arch. Sexual Behav.* **22**, 145–155 (1993).
232. Ross, M. W. & Need, J. A. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch. Sexual Behav.* **18**, 145–153 (1989).
233. Chughtai, B. et al. A neglected gland: a review of Cowper's gland. *Int. J. Androl.* **28**, 74–77 (2005).
234. Alwaal, A., Breyer, B. N. & Lue, T. F. Normal male sexual function: emphasis on orgasm and ejaculation. *Fertil. Steril.* **104**, 1051–1060 (2015).
235. Thakar, R. Is the uterus a sexual organ? sexual function following hysterectomy. *Sex. Med. Rev.* **3**, 264–278 (2015).
236. Smith, Y. L., Van Goozen, S. H., Kuiper, A. J. & Cohen-Kettenis, P. T. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol. Med.* **35**, 89–99 (2005).
237. Wierckx, K. et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J. Sex. Med.* **8**, 3379–3388 (2011).
238. Simonelli, C., Eleuteri, S., Petruccelli, F. & Rossi, R. Female sexual pain disorders: dyspareunia and vaginismus. *Curr. Opin. Psychiatry* **27**, 406–412 (2014).
239. Horbach, S. E. et al. Outcome of vaginoplasty in male-to-female transgenders: a systematic review of surgical techniques. *J. Sex. Med.* **12**, 1499–1512 (2015).
240. Elaut, E., Weyers, S., Hoebeke, P., Stockman, S. & Monstrey, S. in *The Transgender Handbook* (eds Arcelus, J. & Bouman, W. P.) (Nova Science Publishers Inc., 2017).
241. Mitchell, K. R. et al. Painful sex (dyspareunia) in women: prevalence and associated factors in a British population probability survey. *BJOG* **124**, 1689–1697 (2017).
242. Hadj-Moussa, M., Ohl, D. A. & Kuzon, W. M. Jr. Feminizing genital gender-confirmation surgery. *Sex. Med. Rev.* **6**, 457–468 (2018).
243. Frey, J. D., Poudrier, G., Chiodo, M. V. & Hazen, A. An update on genital reconstruction options for the female-to-male transgender patient: a review of the literature. *Plast. Reconstr. Surg.* **139**, 728–737 (2017).
244. Hoebeke, P. B. et al. Erectile implants in female-to-male transsexuals: our experience in 129 patients. *Eur. Urol.* **57**, 334–340 (2010).
245. Cohen-Kettenis, P. T. & van Goozen, S. H. Sex reassignment of adolescent transsexuals: a follow-up study. *J. Am. Acad. Child Adolesc. Psychiatry* **36**, 263–271 (1997).
246. Smith, Y. L., van Goozen, S. H. & Cohen-Kettenis, P. T. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 472–481 (2001).
247. Lobato, M. I. et al. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch. Sexual Behav.* **35**, 711–715 (2006).
248. Cardoso da Silva, D. et al. WHOQOL-100 before and after sex reassignment surgery in brazilian male-to-female transsexual individuals. *J. Sex. Med.* **13**, 988–993 (2016).
249. Johansson, A., Sundbom, E., Hojerback, T. & Bodlund, O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch. Sexual Behav.* **39**, 1429–1437 (2010).
250. Heylens, G., Verroken, C., De Cock, S., T'sjoen, G. & De Cuypere, G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J. Sex. Med.* **11**, 119–126 (2014).
251. Ruppin, U. & Pfafflin, F. Long-term follow-up of adults with gender identity disorder. *Arch. Sexual Behav.* **44**, 1321–1329 (2015).
252. Coleman, E., Bockting, W. O. & Gooren, L. Homosexual and bisexual identity in sex-reassigned female-to-male transsexuals. *Arch. Sexual Behav.* **22**, 37–50 (1993).
253. Philippsohn, S. & Hartmann, U. Determinants of sexual satisfaction in a sample of German women. *J. Sex. Med.* **6**, 1001–1010 (2009).
254. Lewin, B. F.-M. K., Helmius, G., Lalos, A. & Månsson, S. A. *Sex in Sweden - On the Swedish Sexual Life* (The National Institute of Public Health, 2000).
255. Salvador, J. et al. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin. Neurosci.* **66**, 371–372 (2012).
256. Castellano, E. et al. Quality of life and hormones after sex reassignment surgery. *J. Endocrinol. Invest.* **38**, 1373–1381 (2015).
257. Gomez-Gil, E., Zubiaurre-Elorza, L., de Antonio, I. E., Guillamon, A. & Salamero, M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual. Life Res.* **23**, 669–676 (2014).
258. Doornaert, M. et al. Penile reconstruction with the radial forearm flap: an update. *Handchir. Mikrochir. Plast. Chir.* **43**, 208–214 (2011).
259. Terrier, J. E., Courtois, F., Ruffion, A. & Morel Journel, N. Surgical outcomes and patients' satisfaction with suprapubic phalloplasty. *J. Sex. Med.* **11**, 288–298 (2014).
260. Imborek, K. L., Graf, E. M. & McCune, K. Preventive health for transgender men and women. *Semin. Reprod. Med.* **35**, 426–433 (2017).
261. Althof, S. E., Rosen, R. C., Perelman, M. A. & Rubio-Aurioles, E. Standard operating procedures for taking a sexual history. *J. Sex. Med.* **10**, 26–35 (2013).
262. Kingsberg, S. A. Taking a sexual history. *Obstetr. Gynecol. Clin.* **33**, 535–547 (2006).
263. Brotto, L. et al. Psychological and interpersonal dimensions of sexual function and dysfunction. *J. Sex. Med.* **13**, 538–571 (2016).
264. Nusbaum, M. R. & Hamilton, C. D. The proactive sexual health history. *Am. Fam. Physician* **66**, 1705–1722 (2002).
265. Armuand, G., Dhejne, C., Olofsson, J. I. & Rodriguez-Wallberg, K. A. Transgender men's experiences of fertility preservation: a qualitative study. *Hum. Reprod.* **32**, 383–390 (2017).
266. Tracy, J. K. & Junginger, J. Correlates of lesbian sexual functioning. *J. Women' Health* **16**, 499–509 (2007).
267. Gabrielson, A. T., Sartor, R. A. & Hellstrom, W. J. G. The impact of thyroid disease on sexual dysfunction in men and women. *Sex. Med. Rev.* https://doi.org/10.1016/j.sxmr.2018.05.002 (2018).
268. Defreyne, J. et al. Transient elevated serum prolactin in trans women is caused by cyproterone acetate treatment. *LGBT Health* **4**, 328–336 (2017).
269. Sigurjonsson, H., Rinder, J., Möllermark, C., Farnebo, F. & Lundgren, T. Male to female gender reassignment surgery: surgical outcomes of consecutive patients during 14 years. *JPRAS Open* **6**, 69–73 (2015).
270. Al-Tamimi, M. et al. Colpectomy significantly reduces the risk of urethral fistula formation after urethral lengthening in transgender men undergoing genital gender affirming surgery. *J. Urol.* https://doi.org/10.1016/j.juro.2018.07.037 (2018).
271. Gäredal, M. & Orre, C. *"Trygga sammanhang gör mig kåt!": en studie om transpersoners upplevelser och tankar om sex samt behov av kunskaper och insatser rörande sexuell hälsa* (RFSL & RFSL Ungdom, 2011).
272. Kronawitter, D. et al. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur. J. Endocrinol.* **161**, 363–368 (2009).
273. Nota, N. M. et al. Prolactin levels during short- and long-term cross-sex hormone treatment: an observational study in transgender persons. *Andrologia* **49**, e12666 (2017).
274. Traish, A. M., Goldstein, I. & Kim, N. N. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. *Eur. Urol.* **52**, 54–70 (2007).
275. Buvat, J. et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J. Sex. Med.* **8**, 284–293 (2011).
276. Naumova, I. & Castelo-Branco, C. Current treatment options for postmenopausal vaginal atrophy. *Int. J. Women' Health* **10**, 387 (2018).
277. Unger, C. A. Update on gender-affirming treatment for the transgender woman. *Semin. Reprod. Med.* **35**, 442–447 (2017).
278. Basson, R. & Gilks, T. Women's sexual dysfunction associated with psychiatric disorders and their treatment. *Womens Health* https://doi.org/10.1177/1745506518762664 (2018).
279. Bø, K. Pelvic floor muscle training in treatment of female stress urinary incontinence, pelvic organ prolapse and sexual dysfunction. *World J. Urol.* **30**, 437–443 (2012).
280. Seal, B. N. & Meston, C. M. The impact of body awareness on women's sexual health: a comprehensive review. *Sex. Med. Rev.* https://doi.org/10.1016/j.sxmr.2018.03.003 (2018).
281. Giammattei, S. V. Beyond the binary: trans-negotiations in couple and family therapy. *Fam. Process* **54**, 418–434 (2015).
282. Fruhauf, S., Gerger, H., Schmidt, H. M., Munder, T. & Barth, J. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. *Arch. Sexual Behav.* **42**, 915–933 (2013).
283. Gunzler, C. & Berner, M. M. Efficacy of psychosocial interventions in men and women with sexual dysfunctions — a systematic review of controlled clinical trials: part 2 — the efficacy of psychosocial interventions for female sexual dysfunction. *J. Sex. Med.* **9**, 3108–3125 (2012).
284. Berner, M. & Gunzler, C. Efficacy of psychosocial interventions in men and women with sexual dysfunctions — a systematic review of controlled clinical trials: part 1-the efficacy of psychosocial interventions for male sexual dysfunction. *J. Sex. Med.* **9**, 3089–3107 (2012).
285. Knudson, G., Dhejne, C., Murjan, S., DeCuypere, G. & Robbins-Cherry, S. Enhancing sexual function post gender confirming surgery. Presented at the 2nd Biennial EPATH Conference. (2017).
286. Cipolletta, S., Votadoro, R. & Faccio, E. Online support for transgender people: an analysis of forums and social networks. *Health Social Care Commun.* **25**, 1542–1551 (2017).
287. Ybarra, M. L., Mitchell, K. J., Palmer, N. A. & Reisner, S. L. Online social support as a buffer against online and offline peer and sexual victimization among US LGBT and non-LGBT youth. *Child Abuse Negl.* **39**, 123–136 (2015).
288. Selvaggi, G., Dhejne, C., Landen, M. & Elander, A. The 2011 WPATH standards of care and penile reconstruction in female-to-male transsexual individuals. *Adv. Urol.* **2012**, 581712 (2012).
289. von Vogelsang, A. C., Milton, C., Ericsson, I. & Strömberg, L. 'Wouldn't it be easier if you continued to be a guy?'–a qualitative interview study of transsexual persons' experiences of encounters with healthcare professionals. *J. Clin. Nurs.* **25**, 3577–3588 (2016).
290. Sevelius, J. "There's no pamphlet for the kind of sex I have": HIV-related risk factors and protective behaviors among transgender men who have sex with nontransgender men. *J. Assoc. Nurses AIDS Care* **20**, 398–410 (2009).
291. Dhejne, C. & Arver, S. in *Handbook of Clinical Gender Medicine* (eds Schenck-Gustafsson, K., DeCola, P. R., Pfaff, D. W. & Pisetsky, D. S.) (Kager, 2012).
292. Berli, J. U. et al. What surgeons need to know about gender confirmation surgery when providing care for transgender individuals: a review. *JAMA Surg.* **152**, 394–400 (2017).
293. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* 4th edn (American Psychiatric Association, 1994).
294. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 4th edn, text rev. (American Psychiatric Association, 2000).
295. Berli, J. U., Knudson, G. & Schechter, L. Gender confirmation surgery and terminology in transgender health-reply. *JAMA Surg.* **152**, 1091 (2017).

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